Motor milestones, physical activity, overweight and cardiometabolic risk

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Motor milestones, physical activity, overweight and cardiometabolic risk

from birth to adolescence

Silvia I. Brouwer

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CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

The prevalence of childhood and adolescent overweight and obesity has increased worldwide[1]. Childhood overweight and obesity are of clinical interest because obesity tracks into adulthood[2-4] and associates with health problems like metabolic risk factors for cardiovascular disease[4-6]. Low levels of physical activity (PA) are a contributing factor to overweight and obesity[7]. Since, PA tracks from infancy into childhood[8-10], from childhood into adolescence[11-13] and then into adulthood[14-17], early stimulation of PA may also have benefits later in life. One early determinant for PA is motor skill competence. Focusing on early life development of motor skill competence and PA might therefore be useful when developing strategies to prevent overweight and obesity at young age[18,19].

Motor skill competence

One early determinant for PA is motor skill competence. Motor skill competence is the capacity to perform coordinated movements of muscles, that are controlled by the nervous system. Motor skill competence refers to the ability to control bodily movements, from infants' first spontaneous waving and kicking movements to the adaptive control of reaching, locomotion, and complex sport skills in children and adolescents[20]. Motor skill competence can be divided into fine and gross motor skills. Fine motor skills are characterized by the use of smaller muscle groups such as those in the hand and wrist. Examples of fine motor skills are drawing, cutting with scissors and grasping. Gross motor skills involve the use of large muscle groups in arms, legs and torso. Examples of gross motor skills are walking, running, crawling and climbing, throwing and kicking. In infants, gross motor skill competence is often assessed by the age of achievement of motor milestones, like rolling over, sitting without support, crawling on hands and knees, standing and walking without support. In addition to the age of achievement, the motor skill competence can be evaluated as impaired or developed, worse or better, compared to infants of the same age or a reference standard. In children motor skill competence is often assessed by measuring fundamental movement skills. These fundamental movement skills are skills developed during (early) childhood. They are divided in locomotor skills (e.g. crawling, running, jumping, and climbing), object-control skills (e.g. throwing, catching, and kicking) and stability skills (e.g. balancing) and form the foundation for more advanced movements[21].

To illustrate the development during childhood, it is important to explain some theoretical approaches of development. The maturational perspective assumes that the development of characteristics like motor skills or PA, is a function of maturational processes, mainly by the central nervous system[22-24]. The development is assumed to be an innate process driven by a biological and genetic clock, also known as the 'nature' concept. Another theoretical approach focuses on information processing and is based on Bandura's social learning theory[25] and Skinner's behaviorism[26]. According to this perspective, the brain is functioning like a computer that takes up information, processes it and is delivering 'movements' as 'output'. From this perspective, stimuli from the environment are very important for the development of motor skill competence, PA or other characteristics. This theoretical approach is also known as the 'nurture' concept. Then, socio-ecological perspective stresses the interrelationship between the individual, the environment and the task[27]. According to this socio-ecological perspective the development of motor skill competence, PA or other characteristics must be considered as an interaction between internal and external determinants. For example, infants are physiologically able to crawl on average at the age of 10 months, but when these infants are exposed to different surfaces and/or are encouragement by parents or caretakers, the infant may start to crawl earlier in life and develop its motor skill competence more optimally.

Motor skill competence, physical activity and health outcomes

When it comes to understanding the relationships between motor skill competence, PA and health, Stodden *et al.*[28] suggest a conceptual model with a bi-directional and developmentally dynamic relationship between motor skill competence and PA. They suggest that during infancy and early childhood, PA might drive the development of motor skill competence because increased PA provides more opportunities to promote neuromotor development[29]. In addition, more developed motor skills lead to higher levels of PA when children develop. Then this positive interrelationship that lead to higher levels of PA and motor skills may result into healthier outcomes. There is evidence supporting both in this model, although in infants, studies investigating the relation between early motor skill competence and PA or health outcomes are scarce[30]. Prospective studies in infants showed a trend for lower motor skill competence at age 1 and lower levels of objectively measured PA in 2-year-olds[31]. Lower maternally reported motor skill competence at 6 months resulted in lower levels of objectively measured PA in children aged 11–12 years[32]. Furthermore, delayed motor milestone achievement predicts higher sum of skinfolds in later childhood (age 3 years)[33,34]. However, this relation between motor skill competence and overweight can be bi-directional since two prospective studies with infants younger than 18 months of age found that overweight predicted a delay in motor skill competence[35,36].

In contrast to infants there is more evidence in children and adolescents that motor skill competence is related to levels of PA[29,37-40]. However, since these studies are cross-sectional, the direction of the association is not clear. Prospective studies found that lower motor skill competence was a predictor of lower levels of PA in the future[41,42] but the relation between motor skill competence and PA may in fact be bi-directional[43] since it was found that lower levels of moderate-to-vigorous PA (MVPA) gave worse subsequent motor skill competence at older ages[42]. When studying the relation between motor skill competence and health outcomes, motor skill competence may be directly associated with health outcomes like overweight, adiposity, cardiorespiratory fitness (CRF), muscular strength and cardiometabolic risk markers[39,44,45]. But as with the relation between motor skill competence and PA, the direction of the association is unclear.

In brief, it is clear that there are associations between motor skill competence, PA and health outcomes in the way that infants and children who are less skilled in motor competence have lower levels of PA and more negative health outcomes. However, it is not clear at which age these associations appear or if this association is bi-directional and how these factors influence each other over time.

Physical activity, cardiorespiratory fitness and health

Currently, thousands of studies have been published investigating the association between PA and health in adults. Based on more than five decades of epidemiological studies, it is now widely accepted that lower levels of PA are associated with negative effects on a wide range of health outcomes like CRF[32], overweight and obesity[46], type II diabetes[47], cardiovascular disease (CVD)[48], several forms of cancer like breast cancer[49], colon and rectal cancer[50], bladder cancer[51], gastric cancer[52], but also on cognitive function[53]. When using prospective data, lower levels of PA are associated with subsequent chronic diseases in adults[54,55]. In younger populations like adolescents[56-59], children[56-58,60] and even infants[58] lower levels of PA seem to be associated with more negative health outcomes like health-related quality of life, cognitive development, motor skill competence, CRF, obesity, psychosocial and cardiometabolic health, when studied cross-sectional. However, prospective studies in children and adolescents generally show inconsistent findings when investigating the associations between lower levels of PA and health outcomes like adiposity[61-64]. Similar to the association between motor skill competence and PA, the relation between PA and adiposity could be bi-directional since some studies show that adiposity predicts subsequent PA[65-67].

In reality, the relation between PA and adiposity might be influenced by CRF. Furthermore, PA and CRF may influence each other as well as contribute independently to health[68,69]. According to Stoddens's model (2008)[28], children with more developed motor skills and corresponding higher levels of PA, should demonstrate higher CRF. Interestingly there is evidence that part of the cardiometabolic consequences of obesity can be counteracted by good CRF. A recent meta-analysis shows that high CRF strongly reduces the risk for cardiovascular mortality in overweight and obese individuals[70]. Lean people with a low CRF may be even less healthy than obese people with good CRF. This phenomenon is known as the 'fitness-fatness' paradigm. The fitness-fatness paradigm is mainly studied in (older) adults, but also in adolescents and children there is some evidence that higher levels of CRF contribute to healthier cardiometabolic risk even when overweight[71-76]. Thus, on top of wondering if PA drives obesity or the other way around, it is relevant to consider CRF.

Contextual perspective

To understand the development and interrelationships between motor skill competence, PA, CRF and health outcomes, it is important to take a look at the socio-ecological perspective[27]. The socio-ecological approach emphasizes that health studies should focus not only on intrapersonal behavioral factors but also on the multiple-level factors, to take into account factors from the social, physical and policy environment that influence the specific behaviour in question. According to the socio-ecological perspective, temporal changes in motor skill competence and obesity and the relationship between parental PA and child PA is of interest since infants and children spent most of their time during the first years of life with their parents. Although many studies investigated the association between parental PA and child PA, only a few studied young children, and used objective measurements (e.g. accelerometry) to assess PA levels[77-80]. Most studies support the idea that the PA level of parents is associated with the PA of children[77,81-83]. However, not all studies find an association between parental PA and child PA[78,80]. Age of the child, gender of the parent and the child and the way PA is measured might influence possible associations.

Aims and outline of this thesis

The general aim of this thesis is to study how motor skill competence, PA, CRF, weight status and cardiometabolic risk relate to each other during development from infancy to adolescence. To get insight in contextual factors, the relationships between motor skill competence, PA and weight status are studied from a temporal perspective comparing different cohort over time as well as from a social perspective studying parental influence by looking at parental behaviour.

A conceptual framework of this thesis is presented in Figure 1. This framework shows the relations between motor milestones achievement, PA, CRF, weight status cardiometabolic risk and parental PA. For this, three healthy populations within the Netherlands between the ages of 0-16 years are used: Young Netherlands Twin Registry (YNTR)[84], Groningen

Expert Center for Kids with Obesity (GECKO)Drenthe cohort[85] and Tracking Adolescents' Individual Lives Survey (TRAILS)[86].

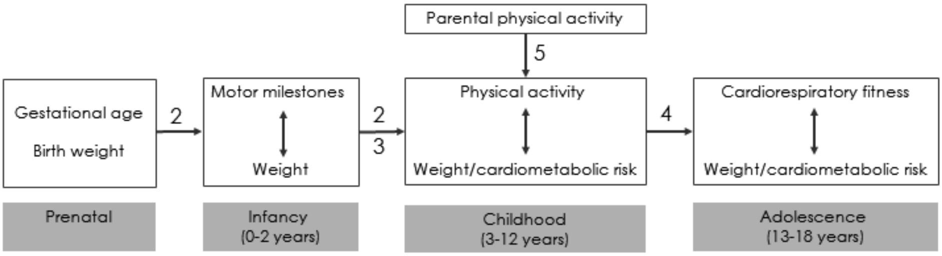

Figure 1 *Conceptual framework showing the relation between early motor milestone achievement, childhood physical activity, cardiorespiratory fitness, parental physical activity, weight status and cardiometabolic risk from infancy to adolescence. The numbers in the figure refer to the chapters of this thesis.*

Chapter 2 gives insights in how early motor milestone achievement is related to subsequent childhood PA, BMI and blood pressure in the GECKO Drenthe cohort. It is hypothesized that infants who are able to walk earlier are more physically active at the age of 5 years and therefore have lower BMI and blood pressure at the age of 5 years. Different intensities (light, moderate and vigorous) of PA are described in relation to BMI and blood pressure.

In **Chapter 3** the relation between motor milestone achievement and weight in children of the YNTR is studied. The aim of this study is fourfold: 1) to examine whether motor milestone achievement and growth has changed over the past twenty years; 2) to study the association between early growth and motor milestones; 3) to study the association between motor milestones and childhood BMI at ages 2, 4, 7 and 10 years; and 4) to examine whether trends in overweight could be explained by trends in age of motor milestone achievement over the past twenty years. Data at different ages of one twin from a twin pair, born between 1987 and 2007, was used.

Chapter 4 explains the importance of good fitness in adolescents, using TRAILS. The purpose of this study was to investigate whether childhood BMI and accelerated growth in BMI from childhood to adolescence are associated with cardiometabolic risk during adolescence and how fitness affects this association. The cardiometabolic risks, measured via a clustered risk score (waist circumference, fasting glucose level, triglycerides, HDL-cholesterol and blood pressure) of boys and girls with high/low increase in fatness from age 11 to 16 years and high/low fitness at age 16 years are compared.

An overview of what types of parental physical activities have an influence on PA levels of their children is studied in **Chapter 5**. The focus in this study is on different types of PA in parents (like leisure time, active commuting) and objectively measured PA in children of the GECKO Drenthe cohort. The effect of gender of the parent and gender of the child is specifically highlighted.

Chapter 6 provides a discussion of the main results in this thesis, methodological considerations, a conclusion and future perspectives.

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CHAPTER 2

LATER ACHIEVEMENT OF INFANT MOTOR MILESTONES IS RELATED TO LOWER LEVELS OF PHYSICAL ACTIVITY DURING CHILDHOOD: THE GECKO DRENTHE COHORT

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ABSTRACT

Background

The aim of this study is to investigate whether age of infant motor milestone achievement is related to levels of physical activity (PA), weight status and blood pressure at age 4-7 years of age.

Methods

In the Dutch GECKO (Groningen Expert Center of Kids with Obesity) Drenthe cohort, the age of achieving the motor milestone 'walking without support' was reported by parents. Weight status and blood pressure were assessed by trained health nurses and PA was measured using the ActiGraph GT3X between age 4 and 7 years.

Results

Adjusted for children's age, sex and the mother's education level, infants who achieved walking without support at a later age, spent more time in sedentary behaviour during childhood and less time in moderate-to-vigorous PA. Later motor milestones achievement was not related to higher BMI Z-score, waist circumference Z-score, diastolic or systolic blood pressure.

Conclusion

The results of this study indicate that a later age of achieving motor milestone within the normal range have a weak relation to lower PA levels at later age. It is not likely that this will have consequences for weight status or blood pressure at 4-7 years of age.

INTRODUCTION

The importance of physical activity (PA) in the early years of life has been documented for a broad spectrum of health benefits, for example improved fitness, motor skill competence, cognitive development, psychosocial health, and cardiometabolic health[1,2]. PA tracks from early childhood into middle childhood[3] and into adulthood[4]. Identifying early life factors that influence childhood PA may help to increase PA in later life. In the long run, this might be important for public health promotion strategies.

One early life factor associated with childhood PA is motor skill competence[5-7]. In children motor skill competence is often assessed by measuring fundamental movement skills like jumping, hopping, running, and throwing. Several cross-sectional studies have shown that children aged 6 to 12 years who have lower levels of motor skill competence tests have lower levels of objectively measured PA and higher levels of sedentary behaviour (SB)[6-8] compared to children who have higher levels of motor skill competence. However, the direction of the association is not clear and the relationship may in fact be reciprocal[9], and dependent on age. On the one hand, as children develop, adequate motor skill competence is of importance for participation in PA[10]. On the other hand, engagement in PA at young age may be important for the development of motor skill competence[11]. Prospective studies are needed but evidence for the direction of this association is scarce, especially in young populations[12]. The association between infant motor skill competence and objectively measured PA later in childhood has only been studied in a population of 2 year-old children[13] and in a 11-12 year-old population[14]. Since only one of the two studies showed a significant association, more clarity is needed whether infants who *develop their motor skills later*, but within the normal range, are less physically active during childhood.

Since PA levels have dropped during the last decennia[15], a focus on infants motor skill competence might help to target inactivity during childhood. In addition to PA, low levels of motor skill competence has also been related to the development of overweight, obesity and blood pressure in children[16-18]. Since low levels of motor skill competence may be related to the development of obesity, the question rises whether this is mediated by lower levels of PA.

To gain more insight in the relation between motor skill competence and PA, we will investigate whether later achievement of the motor milestone 'walking without support' is related to lower levels of PA, and more time spent in SB at later age (4-7 years). Second, we will investigate whether later achievement of the motor milestones 'walking without support' is related to higher weight status and blood pressure, and if so, whether this is mediated by PA.

METHODS

Participants

The GECKO (Groningen Expert Center of Kids with Obesity) Drenthe birth cohort is a population-based birth cohort that has been designed to study the determinants and development of childhood weight status. All parents of children born between April 2006 and April 2007 in the province of Drenthe in the Netherlands were invited to participate in the study. Further details regarding the study design, recruitment and study procedures have been published elsewhere[19].

Child characteristics

Gestational age (GA) and educational level of the mother (low/middle education or higher vocational education) was self-reported. Educational level was reported since it is part of socioeconomic status which is associated with motor skill competence[16]. Anthropometry of children was measured by trained nurses from Youth Health Care according to a standardized protocol when children were 4-7 years old. Weight was measured in light clothing using an electronic scale with digital reading, and recorded to the nearest 0.1kg. Height was assessed using a stadiometer and recorded to the nearest 0.1 cm. Waist circumference (WC) was measured twice using a standard tape midway between the lowest rib and the top of the iliac crest at gentle expiration in standing position to the nearest 0.1 cm. When the two measurements differed more than 1 cm a third measurement was done. BMI was calculated as weight (kg) divided by height squared (m). Gender and age-specific BMI Z-scores and WC Z-scores were calculated using the Dutch growth analyzer software, version 3.5 based on 1997 reference data[20]. Systolic (SBP) and diastolic blood pressure (DBP) (mmHg) were measured using a digital automatic blood pressure monitor (M3 intellisense™, OMRON healthcare Co. Japan) with the smallest cuff. The cuff was placed on the left arm of the relaxed and seated child and the measurements were repeated up to 3 times at one-minute intervals. SBP and DPB Z-scores were calculated considering the child's exact age, height and gender using the fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents as a reference[21].

Motor skill competence and physical activity

Motor skill competence in infants is often assessed by the age of achievement of motor milestones (like sitting, crawling, standing and walking with or without support). We used the motor milestone 'walking without support' since the achievement of different motor milestones follows a fixed sequence for sitting without support, standing with assistance, walking with assistance, standing alone and walking alone) and therefore suggest a correlation[22,23]. Walking without support is considered to be universal, fundamental to the acquisition of self-sufficient erect locomotion, and simple to test and evaluate[24,25]. The question 'at how many months did your child walk without support for the first time' was assessed after the child Youth Health Care visit at 18 months via parents who filled in the surveys. Infants who had not achieved the milestone of walking without support by age 18 months were not included in the analyses. Previous research has shown that retrospective surveys completed by the mother on the infant's gross motor milestones are a reliable source of data[26] although a bias towards earlier dates of achievement are likely (WHO; reliability). Maternal recall and report of infant's milestone achievement has been used in several other studies[27,28]. PA was assessed between 2009 and 2013 when the children were between 4 and 7 years old using the ActiGraph GT3X accelerometer (ActiGraph, Pensacola, FL). The ActiGraph has been shown to be a reliable and valid device for measuring PA volume and intensity in young children[29]. Parents were instructed to have their child wear the ActiGraph on the iliac crest on the right hip with an elastic belt for four consecutive days, including at least one weekend day, during all waking hours except while bathing or swimming. Data were collected at a frequency of 30 Hz. All children who recorded a wearing time ≥840 min/day (14h/day) were checked manually for sleeping time and data were corrected if necessary. ActiGraph non-wearing time was classified as a period of a minimum of 90 minutes without any observed counts[30]. The cut-off points recommended by Butte *et al.*[31] were used to calculate time spent in SB (<240 counts per minute (cpm), light PA (LPA) (241 - 2120 cpm), moderate PA (MPA) (2121 – 4450 cpm), and vigorous PA (VPA) (>4450 cpm). The data were analysed in 15-second epochs[32]. Mean SB, LPA, MPA, and VPA were calculated per child using all days with wear time ≥600 min/day. Moderate to vigorous PA (MVPA) was calculated by summing up the time spent in MPA and VPA. Adherence to the Dutch healthy exercise norm was defined as ≥60 minutes of MVPA per day. To be included in the analysis in this study, the accelerometer had to be worn for at least 600 minutes/day for at least 3 days.

Statistics

Data were analysed using SPSS 23.0. BMI, MPA, VPA, MVPA and total PA were Ln transformed because of skewedness. A two-tailed Student's t-test was used to test for gender differences. Means ± standard deviations or the median (25th, 75th percentile) are presented. To test whether later achievement of the motor milestones 'walking without support' is related to lower levels of PA, and more time spent in SB at later age (4-7 years) we used separate multiple linear regression models to examine associations of age of achievement with each of the PA outcomes (SB, LPA, MVPA and total PA), as continuous variables. We first ran Model 1 for unadjusted analyses examining the relationship between individual motor milestones and each PA outcome. In Model 2 we included exact age of assessment of PA, sex and maternal educational level as covariates. When testing whether later achievement of the motor milestones ‘walking without support’ is related to higher weight status and blood pressure we used the same Model with BMI Z-scores, WC Z-score, DBP Z-score and SBP Z-score as the outcome. Analysis on DBP Z-score and SBP Z-score were additionally adjusted for height. To test whether a possible relation between later achievement of the motor milestones ‘walking without support’ and higher weight status or blood pressure is mediated by PA, we added each of the PA outcomes to the Model. Because data of MVPA and total PA were Ln transformed the β’s do not reflect actual minutes/day MPVA or total PA but reflect Ln transformed results. By filling in the regression analyses we calculated the Ln MVPA for different ages of motor milestones achievement (in months). The amount of minutes/day MVPA corresponding to the outcome of the regression were looked up in the original file to translate it into meaningful data.

RESULTS

In total, parents of 2,997 children expressed the intention to participate in the study, 2,874 of whom actively participated. The flowchart (Fig. 1) shows the GECKO cohort with available data for motor milestones achievement, PA and cardiometabolic risk. The questionnaire for motor milestones achievement was handed out to parents who visited the Well Baby Clinic and for logistic reasons not all parents who actively participated in the study received a questionnaire. The questionnaire was filled in by 1,672 parents. From 1,672 children 7% (n=117) were not able to walk without support at 18 months, 2% (n=39) of the parents filled in the questionnaire but didn’t fill in the question with how many months their child was able to walk without support, and <1% (n=5) filled in implausible data (walking before age 5 months) and were therefore excluded from analyses. The parents of 2,276 children were contacted for PA measurements and 1,475 of these children were measured for PA with an ActiGraph GT3X accelerometer (ActiGraph, Pensacola, FL) between the age of 4 and 7 years. Of those, 1135 children had valid ActiGraph data. There were 666 children with data for both motor milestones and PA and there were in total 502 children who had complete data for motor milestones, PA and cardiometabolic risk.

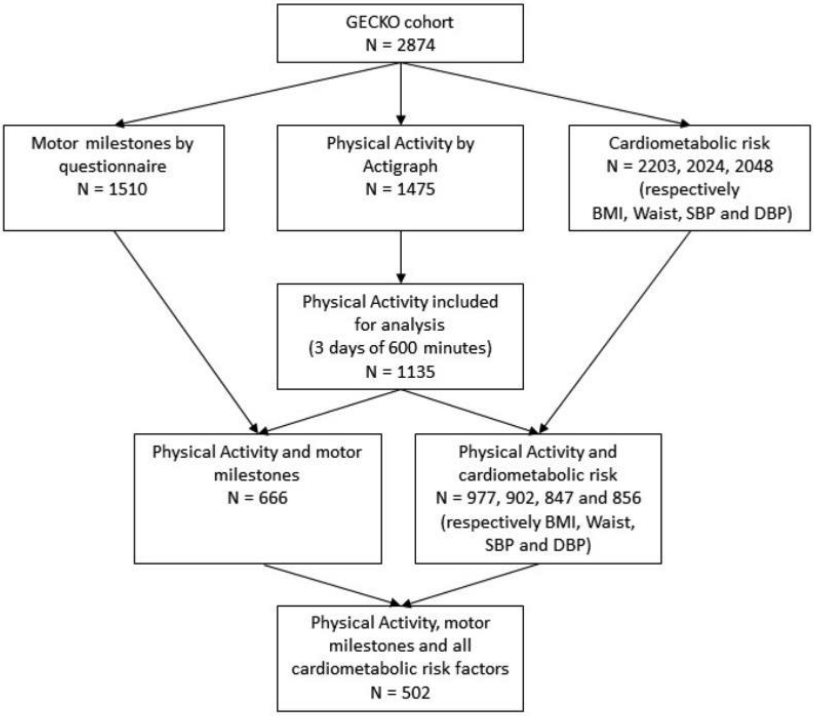

Figure 1 Flowchart of the participants

All participants were recruited from the GECKO Drenthe birth cohort (babies born between April 1st 2006 and April 1st 2007 in Drenthe, Netherlands) and measured for PA between 2009 and 2012 when aged 4-7 years. To check for bias in the study population for parents who did or did not report the age of achievement of the motor milestone 'walking without support', children with data for motor milestones achievement were compared to children without data for motor milestone achievement. Children without data for motor milestone achievement spent 6 minutes per day more in SB compared to children with data on motor milestone achievement (p=0.04). No differences were found in MPA, VPA, MVPA and total PA between these groups. Furthermore, no differences were found between SB and PA levels of children with or without data for BMI, waist, DBP and SBP. To check for a bias the other way around, we tested whether the age of motor milestone achievement differed between children with data ActiGraph data and without ActiGraph data. There were no differences between those groups (p=0.96).

Table 1 presents the baseline characteristics of the population. Children were able to 'walk without support' at the age of 14.1 ± 1.9 months. This age was comparable to the normative sample of the World Health Organization's Multicentre Growth Reference Study[17]. Children born with a shorter GA achieved their moment of walking later compared to children with longer GA (r^2 -0.15; $p<0.001$). Children's PA was assessed on average at 5.8 years. About 50% of children adhere to the Dutch guidelines for PA.

Table 1 Characteristics of the GECKO Drenthe cohort

	Total	**Boys**	**Girls**
Child characteristics			
Gestational age (weeks)(1089)	39.9 ± 1.6	39.8 ± 1.6	39.9 ± 1.5
Age of assessment (years)(1135)	5.8 ± 0.3	5.9 ± 0.3	5.8 ± 0.3
Height (cm)(977)	118.5 ± 5.1	118.8 ± 5.1	118.2 ± 5.0
Weight (kg)(977)	22.5 ± 3.0	22.5 ± 2.8	22.4 ± 3.2
BMI (kg/m^2)(977)	15.8 (15.1, 16.7)	15.8 (15.1, 16.6)	15.7 (15.0, 16.7)
BMI Z-score (SD)(977)	0.2 ± 0.8	0.2 ± 0.7	0.2 ± 0.8
Waist (cm)(902)	54.6 ± 4.3	54.7 ± 4.4	54.5 ± 4.2
Waist Z-score (SD)(902)	0.4 ± 1.0	0.3 ± 1.0	0.4 ± 0.9*
DBP (mmHg)(856)	62.0 ± 8.3	60.7 ± 7.9	62.4 ± 7.5*
DBP Z-score (SD)(856)	0.3 ± 0.7	0.1 ± 0.7	0.5 ± 0.7**
SBP (mmHg)(847)	103.3 ± 9.6	103.8 ± 8.5	103.3 ± 8.5
SBP Z-score (SD)(847)	0.6 ± 0.8	0.5 ± 0.8	0.7 ± 0.8**
Motor milestones and Physical activity			
Age 'walking without support' (months)(666)	14.1 ± 1.9 (7.0-19.0) 14.0 (13.0-15.0)	14.1 ± 1.9 (9.0-19.0) 14.0 (13.0-15.0)	14.0 ± 1.9 (7.0-19.0) 14.0 (13.0-15.0)
Age of assessment (years)(1135)	5.6 ± 0.8	5.7 ± 0.8	5.6 ± 0.8
SB (min/day) (1135)	373.0 ± 55.3	367.5 ± 54.4	379.0 ± 55.6**
LPA (min/day) (1135)	264.9 ± 38.1	264.9 ± 36.5	264.8 ± 39.7
MPA (min/day) (1135)	43.8 (34.7, 54.9)	47.2 (39.3, 59.8)	40.0 (30.9, 48.8)**
VPA (min/day) (1135)	16.7 (11.3, 24.3)	18.6 (12.8, 26.4)	14.7 (10.2, 22.0)**
MVPA (min/day) (1135)	61.3 (47.8, 80.0)	68.1 (53.2, 85.6)	54.5 (42.0, 71.2)**
Total PA (cpm) (1135)	1319.5 (1140.9, 1522.1)	1362.6 (1202.9, 1585.1)	1250.1 (1079.0, 1457.3)**

*Data are presented as means ± sd (with minimum and maximum for age 'walking without support') or median (25th, 75th percentile) and number of participants (n). GA= gestational age , DBP= diastolic blood pressure, SBP= systolic blood pressure, SB= sedentary behaviour, LPA= light physical activity, MPA= moderate physical activity, VPA= vigorous physical activity, MVPA= moderate to vigorous physical activity, Total PA= total physical activity; *significant gender differences p<0.05; **p<0.01*

The associations between motor milestone achievement and PA are presented in Table 2. Model 1 shows that later age of achieving moment of walking was associated with higher SB (β=3.59 [95%CI: 1.37; 5.82]), lower LPA (-2.11 [-3.65; -0.57]), lower Ln MVPA (-0.03 [-0.05; -0.02]) and lower Ln total PA (-0.02 [-0.03; -0.01]). When adjusting for sex, actual age of the child and mother's education level, the associations between motor milestone achievement and PA remain significant for all PA levels: SB (2.73 [0.60; 4.86]), Ln MVPA (-0.03 [-0.05; -0.02]) and Ln total PA (-0.02 [-0.02; -0.01]) except for LPA (-1.40 [-2.85; 0.06]). This means that infants who achieve their motor milestone at a later age spend more time in SB and less time in MVPA, and have lower levels of total PA during childhood. For example, an infant who walks with the age of 12 months spends on average 64.7 minutes per day in MVPA while an infant who walks with 16 months spends on average 56.7 minutes per day in MVPA.

Second, as shown in Model 2, the age of achieving 'walking without support' was not related to relevant health outcomes. Motor milestone achievement was not associated to BMI Z-score (-0.01 [-0.05; 0.02]) or WC Z-score (-0.01 [-0.06; 0.03]), nor to DBP Z-score (-0.02 [-0.06; 0.01]) or SBP Z-score (-0.02 [-0.06; 0.01]). Since motor milestone achievement was not related to most health outcomes, we did not further investigate whether this association was mediated by the level of PA.

Table 2 Later achievement of motor milestone 'walking without support' was related to lower levels of childhood physical activity in the GECKO Drenthe cohort

	SB (min/day)			**LPA** (min/day)			**Ln MVPA** (min/day)			**Ln Total PA** (min/day)		
	β	**B**	**95% CI**	**β**	**B**	**95% CI**	**β**	**B**	**95% CI**	**β**	**B**	**95% CI**
Model 1												
Motor milestone achievement (months)	0.124	3.594	1.369; 5.819	-0.105	-2.109	-3.647; -0.571	-0.156	-0.032	-0.047; -0.016	-0.140	-0.016	-0.025; -0.007
Model 2												
Motor milestone achievement (months)	0.094	2.726	0.595; 4.856	-0.070	-1.394	-2.846; 0.058	-0.160	-0.033	-0.048; -0.018	-0.131	-0.015	-0.024; -0.007

Data are presented as standardized beta coefficients (β), unstandardized B and 95% confidence interval; SB= sedentary behaviour (min/day); LPA= light physical activity (min/day); MVPA= moderate-to-vigorous physical activity (min/day); Total PA= Total physical activity. MVPA and Total PA were Ln transformed because of skewedness. Model 1 shows the unadjusted association between motor milestone achievement and different levels of PA. Model 2 shows the association between motor milestone achievement and different levels of PA adjusting for sex, actual age of the child and maternal education level.

DISCUSSION

In this study, we show that later achievement of the motor milestone ‘walking without support’ is related to lower PA later in childhood. We also show that later achievement of the motor milestone ‘walking without support’ does not seem to have consequences for health outcomes like BMI, WC of blood pressure at the age of 4-7 years.

This study showed that children who achieve their motor milestone later are less physically active during childhood. To our knowledge, and as reviewed by Oglund *et al*.[12], the associations between infant motor skill competence and objectively measured PA later in childhood have only been studied in a population of 2 year-old children[10] and in a 11-12 year-old population[14]. These studies are however well in line with the present findings. The Avon Longitudinal Study of Parents And Children (ALSPAC)[14] showed that infants with lower maternally reported motor skill competence at 6 months had lower levels of objectively measured PA in children aged 11-12 years. A trend towards significance ($p<0.1$) was visible for achieving motor milestones at age 1 and lower levels of objectively measured PA at age 2[13]. Also studies using questionnaire based estimates of PA in children point into the same direction since older age at walking was associated with lower self-reported weekly sport participation in youth aged 14 years[33].

The question rises whether differences in motor skill competence are relevant to differences in PA in children. As explained in the results, an infant who walks without support at the age of 14 months spends on average 4 minutes less in MVPA and 7 more minutes in SB per day compared to an infant who walks without support at 12 months. This means that a child is 28 minutes (7 day/week 4 minutes) per week less active in MVPA when motor milestones are achieved 2 months later. These 28 minutes MVPA per week seem relevant since it has been demonstrated in observational studies that there is a dose-response relationship between PA and health[34]. Participating in as little as 2 or 3 hours of MVPA per week is already associated with health benefits. Therefore, identifying early life determinants of young people’s PA generates meaningful knowledge for future public health interventions, since PA tracks from childhood to adolescence, and then on to adulthood[4,35]. Stimulating motor skill competence in early life may add to the potential strategies available to enhance MVPA. However, enhancing MVPA is not particularly easy, taking into account that the outcomes of most multi-level interventions show minimal to no increases in PA. The review by Ling *et al*.[36] shows that most multi-level interventions with objectively measured PA in young children do not find an effect on PA. From the 20 studies included in the review, just 3 studies found an increase in MVPA, 3 studies found an increase in total PA and 2 studies found a decrease in SB.

Since we found that infants who achieve their motor milestone 'walking without support' at a later age, although within the normal range, had lower PA levels during childhood, we were asking ourselves if variations in achieving motor milestones could be related to variations in health outcomes. We would expect that children with somewhat later motor milestone achievement and lower PA could have a higher BMI and WC, based on evidence that higher levels of PA may lead to healthier outcomes in cross sectional as well as longitudinal studies[37,38]. However, in our study infants who achieve their moment of walking without support later did not have higher BMI or WC during childhood. How can we explain the absence of an association between infant motor skill competence and childhood BMI in our study? In contrast to our findings, there is ample evidence for a relation between motor skill competence and overweight, mostly from cross-sectional studies[37,39]. Most but not all of these cross sectional studies in children and adolescents show that children and adolescents who have lower levels of motor skill competence have a higher BMI. Also in infants, delays in motor skill competence were found more often in overweight compared to normal weight infants[40-42]. These cross-sectional studies cannot account for reverse causation. Motor skill competence may limit PA and thereby increase the risk for overweight, but the other way around, overweight may limit PA and therefore motor skills may be practised less. Prospective studies are necessary to gain more insight. Two prospective studies showed no relationship between delayed motor milestone achievement and BMI at age 3 and 5, but did find an association with higher sum of skinfolds at 3 years of age[43,44]. Furthermore, a randomized controlled trial testing an early life activity stimulation program delivered to parents in Well Baby Clinics showed benefits on adiposity at the age of 2.5 years[45]. Therefore it is possible that there is an association between delayed motor milestone achievement and childhood body composition when other measures of adiposity are used. In general, the association between motor skill competence and adiposity may be bi-directional, and the effects are likely to be small or absent.

The strength of the study is the objective measure for PA in a relative young population and the large size of the population, although in the combination between motor skill competence and PA many motor skill competence data were missing. Furthermore, our study showed that the associations between motor skill competence and PA were consistently present in all PA behaviours except for LPA. The limitations of the study are the use of only motor milestone 'walking without support' as a measure for motor skill competence, since walking is also PA. Therefore it could also be that the association we measure is tracking of PA. We can also not exclude that children who walk earlier may have been stimulated more by parents. We have shown before that activity levels of the parents are related to activity levels of the children[46]. Only infants who reached their motor milestone 'walking without support' within the normal range of development, were included in this study. Therefore, it is not possible to make any statements about clinical motor delays.

Conclusion

The results of this study indicate that a later age of achieving motor milestone within the normal range have a weak relation to lower PA levels at later age. It is not likely that this will have consequences for weight status or blood pressure at 4-7 years of age.

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CHAPTER 3

INFANT MOTOR MILESTONES AND CHILDHOOD OVERWEIGHT: TRENDS OVER TWO DECADES IN A LARGE TWIN COHORT

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ABSTRACT

Background

Poor motor skill competence may influence energy balance with childhood overweight as a result. To investigate whether the age of motor milestone achievement has changed over the past decades and whether this change may contribute to the increasing trend observed in childhood overweight.

Methods

Motor skill competence was assessed in children from the Young Netherlands Twin Register born between 1987 and 2007. Follow-up ranged from 4 up to 10 years. Weight and height were assessed at birth, 6 months, 14 months, and 2, 4, 7 and 10 years.

Results

Babies born in later cohorts achieved their motor milestones 'crawling', 'standing' and 'walking unassisted' later compared to babies born in earlier cohorts (n=18,514, p<0.001). The prevalence of overweight at age 10 was higher in later cohorts (p=0.033). The increase in overweight at age 10 was not explained by achieving motor milestones at a later age and this persisted after adjusting for gestational age, sex, and socioeconomic status.

Conclusion

Comparing children born in 1987 to those born in 2007, we conclude that children nowadays achieve their motor milestones at a later age. This does not, however, explain the increasing trend in childhood overweight.

INTRODUCTION

Over the past decades the prevalence of overweight and obesity has increased in children[1]. Childhood overweight is of clinical interest because it tracks into adulthood[2,3], and it associates with metabolic risk factors for cardiovascular disease[4].

According to the developmental approach of Stodden[5], the potential role of motor skill competence may promote physical activity and weight status. Therefore, motor skill competence may be one factor that explains the changes in energy balance over time, with childhood overweight as a result[6]. There are signs that motor skill competence is declining[7-9], but literature is sparse. Several factors may play a role. For example, to reduce the chance of sudden infant death syndrome, parents are recommended since 1987 to let their baby sleep on their back or side, instead of on their tummy. However, tummy time aids in developing neck, shoulder, and core strength which increases the development for other motor milestones[10]. Also the arrival of equipment like maxi-cosies, babywalkers and screens like television and i-pads may play a role[11,12].

Several studies describe the relationship between motor skills and overweight. In infants aged below 24 months overweight is more often reported in those who reach their motor milestones at an older age[13,14]. Although these studies provide evidence for an association between motor skill competence and overweight, cause and consequence are uncertain, because the association can be bi-directional. On the one hand it is possible that lower scores on motor skill competence may cause overweight by not having the opportunities to be more physically active and thereby spend more energy. On the other hand, overweight may cause lower scores on motor skill competence since overweight may hinder movement. Prospective studies on the association between motor skill competence and overweight in children show that lower scores on motor skill tests are associated with increased BMI[15,16] suggesting causality. For infants, the situation is somewhat different. Infants may have more difficulty in starting to walk when they have a higher body weight-for-length, because it takes more strength. On the other hand, if they have developed faster and stronger, a higher body weight may indicate better growth and muscle mass, and this may favour achievement of motor milestones. Indeed, there is some evidence for associations in both directions. Although babies with lower birth weight (BW) seem to reach their motor milestones later compared to those with higher BW[17,18], two prospective studies with infants younger than 18 months found that overweight predicts lower scores on motor skill tests[14,19]. In addition, lower scores on motor skill tests predicts a higher sum of skinfolds in later childhood (age 3 years)[20] but no relation was found between time of achieving motor milestones and BMI at the age of 7[18]. The results are thus inconclusive which warrants further investigation. One way to address this question is to look at trends in achievement of motor milestones and overweight over time, using a cohort effect approach.

The aim of our study was 4-fold: 1) to examine changes over the past twenty years in motor milestone achievement and growth in body weight (weight-for-length, BMI and overweight) by comparing children from birth years 1987 to 2007; 2) to study the association between early growth (weight-for-length) and the age that infants achieve motor milestones; 3) to study the association between motor milestones and childhood BMI at ages 2, 4, 7 and 10 years; 4) to examine whether changes in overweight could be explained by later motor milestone achievement. Data from twins participating in the Young Netherlands Twin Register (YNTR) were used to address these aims, because the YNTR is a unique cohort with a continues influx of new-born twins since 1987.

MATERIALS AND METHODS

Population: Data from twins participating in the Young Netherlands Twin Register (YNTR) were analysed in this study. The YNTR was established in 1987 as a population-based volunteer register. It recruits families with twins a few months after birth and registers around 40% (ranging from 38 to 53% over the years) of all multiple births in the Netherlands[21]. Prospective data have been collected for twins since 1987 through age-specific surveys in which parents provide data on development and health. Since data from children from the same family are dependent, one twin from each pair was selected randomly. Inclusion criteria were available data on motor milestones and BW and gestational age (GA). Exclusion criteria were preterm birth (<32 weeks), very low BW (<1500 grams) and disability or illness which interferes with daily functioning. All data used in the analyses were collected under protocols that have been approved by the appropriate ethics committees, and this study was performed in accordance with the ethical standards from the 1964 Declaration of Helsinki and its later amendments.

Table 1 Data collection of twins from the Young Netherlands Twin Register (YNTR)

	Survey
Age 0-6 months	Pregnancy and birth
	Table for keeping track on motor milestones
Age 2 years	Growth and motor milestone achievement
Age 4-10 years	Growth and socioeconomic status

Birth data: After registration of new-born twins, mothers received an initial survey with items on pregnancy and birth. Mothers provided information on GA, BW, and length. To support keeping track of motor milestones, a table was attached to the first survey for parents to enter data when motor milestones were reached (Table 1).

Age 0- 2 years: A second survey on growth and motor milestone achievement was sent at age 2. Parents were asked to record when motor milestones were reached: rolling over from back to belly, sitting without support, crawling on hands and knees, standing without support, walking without support and speaking for the first time. Obtaining data on motor milestone achievement by mail using retrospective surveys on children turning 2 years of age has been shown to be a reliable method[22]. In a validation study, data for motor milestones conducted via monthly telephone interviews from 217 twin pairs were compared to retrospective mail surveys from 463 twin pairs born in the same year. Motor milestone achievement reported by monthly telephone interviews showed no differences compared to retrospective data from mail surveys. For data on growth, parents of twins were asked to provide the report with growth data measured by nurses from the Youth Health Services from birth to age 2 (13 visits until the age of 2 years: 4 and 8 weeks, 3, 4, 6, 7.5, 9, 11, 14 and 18 months, 2 and 3 years, 3 years and 9 months). For this study growth data of BW, 6 months (prior to the mean age of achieving the first of motor milestone), 14 months (just before mean age of achieving the last motor milestone) and 2 years are used.

Age 4-10 years: For the growth data on 4, 7 and 10 years, length and weight were reported in age-appropriate questionnaires[21]. Growth data for 4 years were obtained in the same way as growth data between birth and age 2. Growth data for 7 and 10 years was measured by parents.

Socio economic status: Parents were asked to report the family socio economic status (SES) measured as highest parental occupation at ages 4, 7, and 10 of their twins. Family SES was scored in five different categories that approximately translate to: 1) 'Unskilled labor'; 2) 'Job for which lower vocational education is required'; 3) 'Job at medium level'; 4) 'Job at college level' and 5) 'Job at university level'[23].

Data calculations: For weight and length until age 14 months, weight-for-length (WfL) standard deviation scores (SDS) were calculated using the Growth Analyzer 3 software package, with the Dutch reference growth charts for the general population from 1997[24]. A score below 0 means having a lower WfL compared to the reference group and a score above 0 means having a higher WfL compared to the reference group. BMI at age 2, 4, 7 and 10 years was calculated as weight (kg) divided by length (m) squared. Standard deviation scores were calculated using the same software package. Linear interpolation was used to reduce the amount of missing data as follows: missing data for BMI SDS at age 2 years were interpolated based on the BMI SDS at age 14 or 18 months and at 3 years; missing data for BMI SDS at age 4 years were interpolated based on the BMI SDS at age 2 or 3 years and 5 or 7 years; missing data for BMI SDS at age 7 years were interpolated based on the BMI SDS at age 4 or 5 years and at 10 years. For age 2, 4 and 7 years 1467 (10.7%), 2410 (33.5%) and 1027 (14.3%) data points respectively were interpolated this way. Most of the data missing at 10 years is because children born in the latest cohorts did not reach the age of 7 or 10 years during the study yet. They have a shorter follow-up and therefore the amount of children with growth data at age 7 and 10 is lower compared to the number of children at younger ages. Children were classified as overweight or obese using Cole's extended international body mass index cut-offs classification[25].

Data analyses: SPSS 20.0 was used for the analyses. Infants were subdivided into seven birth cohorts (1987-1989, 1990-1992, 1993-1995, 1996-1998, 1999-2001, 2002-2004, 2005-2007). To examine differences for motor milestone achievement, GA, BW, birth length, WfL SDS and BMI SDS across birth cohorts an ANOVA was used. The chi-square was used to test the differences in prevalence of overweight (yes, no) age 4, 7 and 10. To study the association between early growth and motor milestones multiple linear regression analysis was used with the different motor milestones as the dependent and BW, WfL age 6 or 14 months as the independent. The analyses were adjusted for GA, exact age during measurement of growth, sex, socioeconomic status (SES) and cohort. To study the association between motor milestones and childhood BMI SDS at ages 2, 4, 7 and 10 years linear regression analyses was used with BMI SDS at ages 2, 4, 7 or 10 years as the dependent and the different motor milestones as the independent while adjusting for GA, exact age during measurement of growth, sex, socioeconomic status (SES) and cohort. Regression coefficients (β values) and 95% confidence intervals (CI) are reported. To examine whether an increase in overweight prevalence could be explained by later motor milestone achievement logistic regression was used with overweight (yes/no) at age 2, 4, 7 or 10 years as the dependent variable. In our first model, cohort was used as the independent. In our second model we adjusted for the covariates GA, exact age during measurement of WfL or BMI, sex, socioeconomic status (SES). In our third model 'moment of walking' was added. In the fourth model the interaction between 'moment of walking' and cohort was added. Within the results and discussion we mainly use the term infants and/or children to refer to our twin population.

RESULTS

In total, data for 20,367 children from the Netherlands Twin Register were included. Infants without data on GA or BW, with preterm birth (<32 weeks GA) or with very low BW (<1500g) were excluded (n=1,625, 8%). Infants with a disability or illness which interferes with daily functioning were also excluded (n=22, 0.1%). A total of 18,514 individuals remained for the final analyses.

In Table 2, the characteristics of the children are shown. Mean GA was 37 ± 2.0 weeks. At 6 and 14 months, the infants in this study had a negative mean WfL SDS, indicating that mean WfL was lower than for the reference group (general population). Mean BMI-for-age at 2, 4, 7 and 10 years were all negative (between -0.1 and -0.4 SD) and therefore lower compared to the reference group. An ANOVA showed that there were no differences in WfL SDS age 6 and 14 months and BMI SDS at age 2, 4, 7 or 10 years between children with 0 till 6 missing values on growth. However, there was a linear association between missing data and GA and BW in the way that children with more missing data (0 till 6) on growth had shorter GA ($p<0.001$) and weighed less compared to children with less missing data on growth ($p<0.001$).

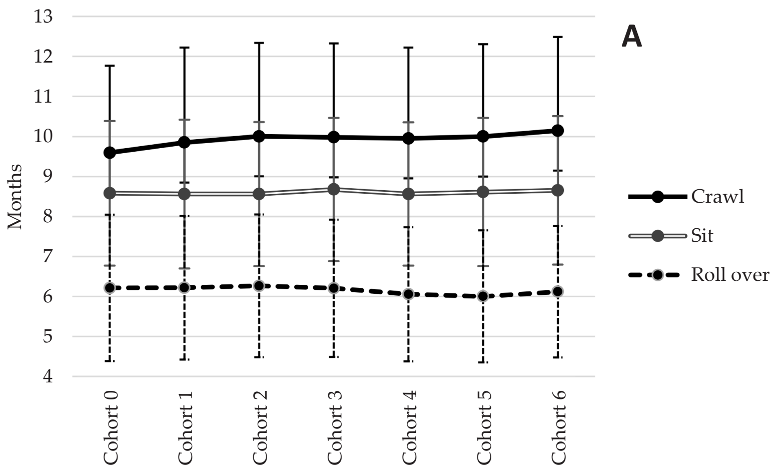
Cohort effects

GA decreased between 1987 and 2007 from 37.4 weeks in the first cohort to 36.8 weeks in the last cohort ($p<0.001$), as reported before[26]. A decrease in GA from 1987 to 2007 was not accompanied with a decrease in BW, indicating a general trend towards higher BW for a given GA. Although in this study preterm birth (<32 weeks) were excluded, changes in BW depended on GA: up to 32 weeks, birthweight decreased and after 32 weeks birthweight increased[26]. Although there was a significant cohort effect for the age at which 'rolling over' was achieved (Fig. 1A; $p<0.001$), there was no specific linear time trend for an increase or decrease but infants in cohort 4 and 5 reached the moment of rolling over earlier compared to infants form the other cohorts. Infants born in the last cohort achieved crawling, standing and walking later than infants born in the earlier cohorts (Fig. 1A + B; $p<0.001$). This linear trend was most pronounced for the motor milestones 'standing without support' and 'walking without support'. Infants born in 1987-1989 reached these milestones almost one month earlier than infants born in 2004-2007 (from 11.7 ± 2.4 to 12.6 ± 2.6 months for standing without support and from 14.5 ± 2.1 to 15.3 ± 2.4 months for walking without support). The 'first word spoken' also differed across cohorts (Fig. 1B; $p<0.001$) but showed an opposite linear trend. Infants born in the latest cohorts spoke their first word earlier than those born in the earlier cohorts, with the exception of the first cohort. WfL SDS at age 6 and 14 months and BMI SDS age 2 (Fig. 1C), 4 and 7 years (Fig. 1D) showed significant differences across cohorts (respectively $p<0.001$; $p<0.001$; $p=0.010$; $p<0.001$; $p=0.043$) but there was no obvious linear trend in any direction with exception for BMI SDS age 4 years. At the age of 4 years, BMI SDS was lowest in cohort 2 and increased from cohort 2 to cohort 6. However, there were no significant differences between the first and last cohort for BMI SDS age 4 years. With regard to the prevalence of overweight (yes/no), an increase in the prevalence of overweight was observed at the age of 10 years (χ^2(df=4, n=5325)=10.457; $p=0.033$) but not at age 4 or 7 years (Fig. 1E).

Table 2 Baseline descriptives of twins from the Young Netherlands Twin Register (YNTR)

	Birth	6 months	14 months	2 years	4 years	7 years	10 years
Infants							
Total (N)	18514	15619	12998	12261	6793	6152	5325
Girls, (N)	9282	7857	6568	6186	3461	3176	2750
Gestational age (weeks)	37.0±2.0	-	-	-	-	-	-
Age (years)		0.5 ± 0.0	1.2 ± 0.1	2.1 ± 0.2	3.9 ± 0.2	7.3 ± 0.3	10.0 ± 0.5
Anthropometrics							
Weight (kg)	2.6 ± 0.5	7.1 ± 0.8	10.1 ± 1.1	12.6 ± 1.5	16.6 ± 2.1	25.1 ± 4.0	33.8 ± 6.1
Length (cm)		65.5 ± 2.7	77.5 ± 3.1	88.3 ± 3.8	104.3 ± 4.4	127.6 ± 6.0	143.2 ± 7.1
WfL (SDS)		-0.05 ± 0.98	-0.09 ± 0.93	-	-	-	-
BMI (kg/m^2)		-	-	16.2 ± 1.3	15.2 ± 1.3	15.4 ± 1. 8	16.4 ± 2.2
BMI-for-age (SDS)		-	-	-0.10 ± 1.02	-0.32 ± 1.03	-0.40 ± 1.06	-0.31 ± 1.10
Overweight /obese (%)*		-	-	-	5.4	7.7	8.2

*Population totals are presented in numbers; Gestational age, age at day of measurements and anthropometrics are presented as means ± standard deviation. WfL (weight-for-length)and BMI-for-age are presented as standard deviation scores (SDS) and overweight/obese as percentage. *Children were classified as overweight or obese using Cole's extended international body mass index cut-offs classification*[25].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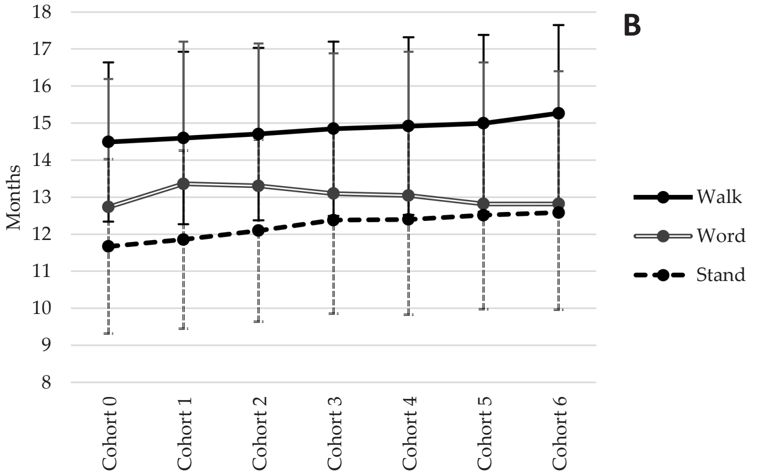
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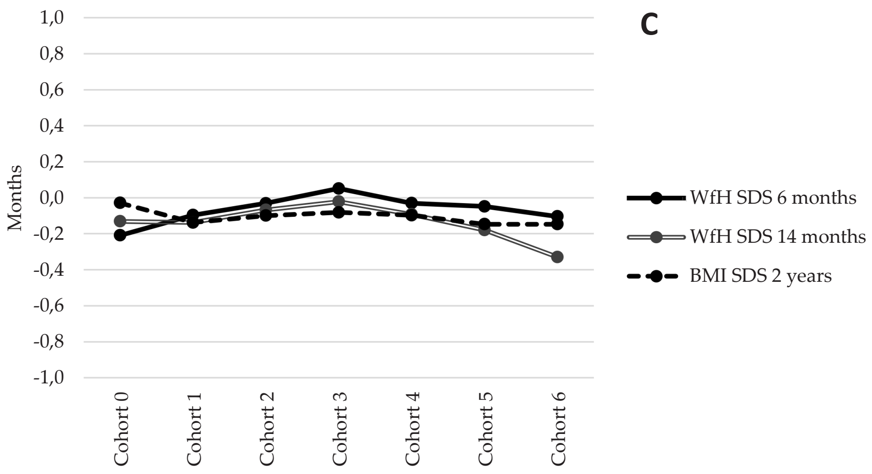
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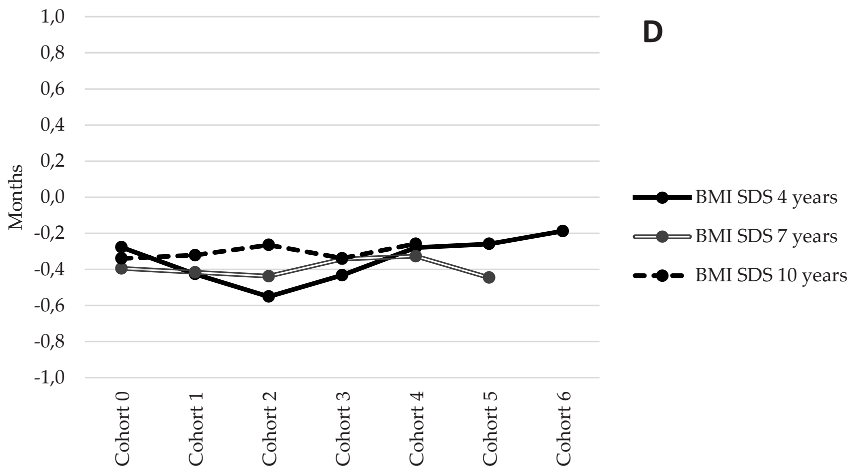

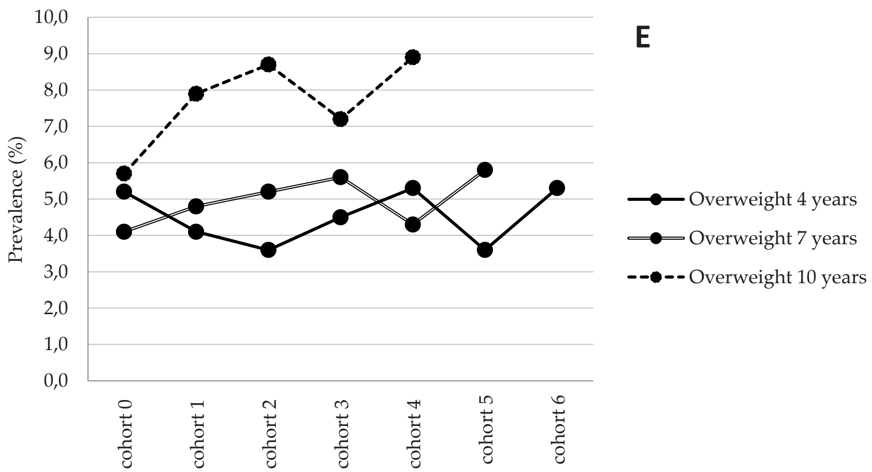

***Figure 1**: Cohort-specific means and standard deviations for motor milestones (A) rolling, sitting, crawling, (B) standing, walking and speaking the first word and (C) WfL SDS age 6, 14 months and BMI SDS at 2 years (D) BMI SDS at 4, 7 and 10 years and (E) prevalence overweight at age 4, 7 and 10 years in twins from the Netherlands Twin Registry (NTR).*

Association between BW and early Weight-for-Length and motor milestone achievement

First, we investigated whether body weight at very young age is a determinant for achieving milestones later, from the perspective that with a higher weight, movements may take more effort and thereby may be related to a later onset of weight carrying movements. Table 3 shows that a lower BW is associated with achieving all motor milestones later (Rolling: β=-0.235 [95%CI: -0.311; -0.160] p<0.01; Sitting: β=-0.130 [-0.208; -0.052] p<0.01; Crawling: β=-0.125 [-0.228; -0.023] p<0.01; Standing: β=-0.157 [-0.266; -0.048] p<0.01), except for 'walking without support'. Infants with a relatively low weight for their length SDS at age 6 or 14 months reached most but not all motor milestones later compared to infants with higher WfL SDS at age 6 (Sitting: β=-0.148 [-0.179; -0.117] $p<0.01$; Standing: β=-0.099 [-0.143; -0.055] $p<0.01$; Walking: β=-0.111 [-0.151; -0.071] $p<0.01$) or 14 months (Sitting: β=-0.149 [-0.185; -0.112] $p<0.01$; Crawling: β=-0.063 [-0.111; -0.016] $p<0.01$; Standing: β=-0.150 [-0.201; -0.099] $p<0.01$; Walking: β=-0.165 [-0.212; -0.119] $p<0.01$). An exception is made for 'rolling over'. For 'rolling over' there was an association in the other direction at age 6 months, in the way that infants with higher WfL SDS reached their moment of rolling over later (β=0.055 [0.025; 0.085] $p<0.01$). All these analyses were adjusted for GA, gender, exact age of assessment, SES and cohort.

Association between motor milestone achievement and childhood overweight at age 2, 4, 7 and 10 years

Next, the association was studied from the other perspective, that it is possible that later achievement of motor milestones may be associated with overweight at later ages, based on the assumption that lower scores on motor skill competence is related to lower levels of PA and therefore less energy expenditure. In general, later achievement of motor milestones is related to lower values for BMI SDS. This was significant for 'sitting without support' for all ages (Age 2: β=-0.023 [-0.033; -0.012] $p<0.01$; Age 4: β=-0.019 [-0.033; -0.005] $p<0.01$; Age 7: β=-0.032 [-0.046; -0.018] $p<0.01$; Age 10: β=-0.039 [-0.056; -0.021] $p<0.01$) and for the all other milestones with BMI SDS at 7 (Crawling: β=-0.012 [-0.023; -0.001] $p<0.05$; Standing: β=-0.023 [-0.033; -0.012] $p<0.01$; Walking: β=-0.024 [-0.035; -0.013] $p<0.01$) and 10 years of age (Crawling: β=-0.016 [-0.030; -0.003] $p<0.05$; Standing: β=-0.029 [-0.042; -0.017] $p<0.01$; Walking: β=-0.031 [-0.045; -0.018] $p<0.01$). Again the exception is for 'rolling over'. At age 2 years and not age 4, 7 and 10 years, infants who achieve the moment of rolling later have higher BMI SDS (β=0.014 [0.003; 0.025] $p<0.05$) (Table 4). The analyses were repeated on the original data. No differences were found between the results of the interpolated data and the original data with exception of the association between the motor milestone 'walking' and BMI age 4 years. In the interpolated data only a trend was visible (β=-0.009 [-0.020; -0.001] $p<0.08$) and in the original data this association was significant (β=-0.014 [-0.026; -0.003] $p<0.01$).

To determine whether changes in motor milestone achievement over two decades may partly explain the growing prevalence of overweight at age 10, the logistic linear regression showed that this increase in overweight over cohorts could not be explained by the later achievement of motor milestones when adjusting for GA, exact age during measurement of WfL or BMI, sex, socioeconomic status (SES) (β=-0.043; p=0.068).

Table 3 Associations between birth weight, Weight-for-Length SDS at 6 and 14 months and motor milestones

		Rolling		Sitting		Crawling		Standing		Walking	
Age of achievement	months	6.2 ± 1.7		8.6 ± 1.8		9.9 ± 2.3		12.2 ± 2.5		14.8 ± 2.3	
Birth weight (grams)	birth	-0.235	[-0.311; -0.160]**	-0.130	[-0.208; -0.052]**	-0.125	[-0.228; -0.023]**	-0.157	[-0.266; -0.048]**	-0.085	[-0.184; 0.015]
Weight-for-Length SDS	6 months	0.055	[0.025; 0.085]**	-0.148	[-0.179; -0.117]**	-0.030	[-0.071; 0.011]	-0.099	[-0.143; -0.055]**	-0.111	[-0.151; -0.071]**
	14 months	0.016	[-0.007; 0.063]	-0.149	[-0.185; -0.112]**	-0.063	[-0.111; -0.016]**	-0.150	[-0.201; -0.099]**	-0.165	[-0.212; -0.119]**

*Data are presented as mean ±SD or β and 95% confidence interval and are adjusted for GA, actual age, sex, SES and cohort; *p<0.05,** p<0.01*

Table 4 Associations between motor milestones and BMI SDS at 2, 4, 7 and 10 years

Age of achievement	months	BMI SDS							
		age 2 years		age 4 years		age 7 years		age 10 years	
Rolling	6.2 ± 1.7	0.014	[0.003; 0.025]*	0.012	[-0.002; 0.026]	-0.001	[-0.016; 0.014]	-0.011	[-0.029; 0.007]
Sitting	8.6 ± 1.8	-0.023	[-0.033; -0.012]**	-0.019	[-0.033; -0.005]**	-0.032	[-0.046; -0.018]**	-0.039	[-0.056; -0.021]**
Crawling	9.9 ± 2.3	0.001	[-0.007; 0.009]	0.000	[-0.010; -0.010]	-0.012	[-0.023; - 0.001]*	-0.016	[-0.030; -0.003]*
Standing	12.2 ± 2.5	-0.003	[-0.010; 0.005]	-0.013	[-0.022; -0.003]**	-0.023	[-0.033; -0.012]**	-0.029	[-0.042; -0.017]**
Walking	14.8 ± 2.3	-0.005	[-0.013; -0.003]	-0.009	[-0.020; -0.001]	-0.024	[-0.035; -0.013]**	-0.031	[-0.045; -0.018]**

*Age of achieving motor milestones is presented as mean ±SD. BMI standard deviation scores (SDS) are presented as β and 95% confidence interval and are adjusted for GA, actual age, sex, SES and cohort; *p<0.05, **p<0.01*

DISCUSSION

Comparing children born in 1987 to those born in 2007, we conclude that children nowadays achieve their motor milestones at a later age. Over the same era, overweight at age 10 tended to increase with time. The later age of motor milestone achievement did not, however, explain the increasing trend in childhood overweight. Furthermore, WfL and BMI-for-age SDS at different ages did not increase in twins born between 1997-2007. In contrast to what was expected, infants with lower BW and WfL at ages 6 and 14 months reached their motor milestones slightly but significantly later compared to heavier infants, and infants who reached their motor milestones later have slightly but significantly lower BMI.

The later achievement of motor milestones found in this twin population was for the motor milestones crawling, standing and walking and not for rolling and sitting. The findings in the first cohorts, 1987 to 2001, of the YNTR population were published earlier[9] and our present study shows a consistent linear trend which continues until 2007. The later achievement of motor milestones was most pronounced for standing and walking without support. Infants born in 2007 achieved standing and walking on average one month later than infants born in 1987. Although the stability over time in age of motor milestone achievement we found in twins for rolling and sitting is similar to the stability found over twenty years in singletons by Darah *et al*. (2013)[27], the later achievement of other motor milestones we found in twins was not found in another study in singletons by Darah *et al.* (2014)[28]. Differences in how and when motor skill competence is measured could explain the differences in outcomes. The authors used the Alberta Infant Motor Scale (AIMS)[29]. The AIMS does not report the actual age a motor milestone is achieved. Instead, the infant is observed at a specific moment to determine whether he or she is able to perform various motor actions. It is therefore more difficult to detect a change in age of achievement. Furthermore, the AIMS does not observe motor skill competence after standing with support and does not evaluate crawling. Our study found delays in motor skill competence specifically in crawling, standing and walking without support. It is possible that delays are only latent in later motor milestone which were measured by our study but not by Darah *et al*[28]. With regard to the use of data of twins, the comparison on motor milestone achievement between twins and singletons must be discussed. We expect that the outcomes can be generalized towards singletons because within the normal window of achievement of motor milestones there are no major differences between twins and singletons, as we have shown before[9]. Differences in the age of milestone achievement, are mainly explained by the shorter GA of twins. Therefore, when studying motor milestones in our twin population, we adjusted for GA. Furthermore, babies born pre-term (before 32 weeks of GA) or with very low BW (<1500 grams) are considered at risk for motor development deficits[30] and are not included in our studies. Although no other studies were found investigating a cohort trend in motor skills competence in infants, there is support for a decrease in motor skills competence in older populations. Pre-schoolers as well as school-aged children born in later cohorts score lower on motor skill competence than children born in earlier cohorts[7,8]. Since motor skill competence tracks across time[31] the delay in motor milestone achievement we found in twins is in line with decreased motor skill competence scores in older populations[7,8].

It seems clear that children develop their motor skill later nowadays than 20 years ago. The explanation may be found in the guideline to avoid prone position during sleep, to reduce the risk of sudden infant death. Indeed infants with more time in prone position during sleep or being awake reach their motor milestones earlier[32,33]. It may also be related to changes in our transportation habits, as it seems that restriction to move freely in infants could be the reason for later achievement of motor milestones[34,35].

The question that rises is how this affects the activity level and health of the children. Our study shows that babies with lower BW achieve rolling, sitting, crawling and standing later than those born with higher BW. The associations were weak but consistent for all motor milestones except walking. The consistency in the associations strengthens the conclusion that babies with lower BW achieve their motor milestones later compared to heavier babies. Comparable results for an association between lower BW and later age of achieving motor milestones were found in the WHO child growth standards which collected data on motor milestones of 816 infants from six different countries[36], the Northern Finland birth cohort[17] and the Danish National Birth Cohort[18]. It can be concluded that babies with lower BW reach their milestones later compared to babies with higher BW after adjusting for GA. When investigating associations between weight status after birth but before or during all motor milestones are reached, we found that lower WfL at age 6 and 14 months was associated with later achievement of motor milestones. These results are in line with the results found in the Danish cohort[18] but is in contrast with the study of Slining *et al.* (2010)[37] which found that thicker skinfolds were associated with later achievement of motor milestones. Prospective associations between early growth and later motor skill competence seem limited or absent.

Since several studies found that, based on BMI, overweight children score lower on motor skill competence test compared to normal weight children[38-40], but evidence from prospective studies do not show consistent evidence for an association between motor skill competence and overweight[15,16,18,20], we expected that infants who reach their motor milestones later would have higher BMI during childhood. In contrast we found that infants who reach their motor milestones later have slightly lower BMI-for-age SDS at ages 2, 4, 7 and 10 years. Since other prospective studies are performed in population with different ages, we compared our study specific with studies measuring motor skill competence during infancy. This association between later achievement of motor milestones and lower BMI at later age was also found in The Northern Finland birth cohort study[17]. In this study BMI at age14 years that was slightly lower in those who achieved their moment of walking later. In addition, in a large Danish cohort later achievement of motor milestones was associated with slightly lower BMI at age 7 years[18]. In another population late achievers had smaller WfL at age 3 years which are in line with our study[20]. However, the authors showed that late achievers had higher adiposity when measured by skin-fold thickness. The authors suggest that BMI is arguably not sensitive enough to detect associations between anthropometrics and motor skill competence because skinfolds thickness has better associations with body fat compared to BMI[41]. Although we found significant associations between motor milestones and subsequent BMI, the association was small and clinically not relevant. Together with previous studies[11,12,42], we suggest no association between motor milestones and subsequent BMI during childhood.

Regarding the worldwide increase in overweight in children[1], it is noteworthy that our study only showed a minimal increase in overweight at age 10 years. The decrease in GA from 1987 to 2007 was not accompanied with a decrease in BW, indicating a general trend towards higher BW for a given GA. This is in line with the increases of BW of singletons in the same period (1989-2006)[43]. This study shows that BMI in twins at ages 2, 4, 7 and 10 seems relatively stable over the last twenty years. The prevalence of overweight and obesity in this study at ages 4, 7 and 10 is lower than for reference populations[44]. It is known that there are differences in length/height, weight and BMI between twins and singletons which decline with increasing age but do not disappear completely[45-47]. This could partly explain the lower than expected prevalence of overweight during childhood.

Strength and limitations

The strength of our study is the large population with data available for motor milestone achievement in different cohorts (born between 1987-2007) and a follow-up up to 10 years for >5000 children. The limitation is that not for all children weight status was available at all time points. Children with more missing data on weight status had shorter GA and lower BW which could have caused a bias in the way that these children were more at risk for divergent growth patterns. In addition, only twins participated in our study. Although there are differences in growth between singletons and twins[45-47], we do not expect that these differences could affect our conclusions since the associations between motor milestones and growth were clinically not relevant and comparable to studies in singletons. It is known that babies born with lower BW are at higher risk for developing overweight[48]. However, this is normally for babies born with (very) low BW which we excluded from our study. Furthermore, including maternal characteristics like age, BMI and way of conceiving, might be of interest but are currently outside the scope of the present paper.

Conclusion

In conclusion, infants born in later cohorts achieve their motor milestones later than infants born in earlier cohorts. The achievement of motor milestones is minimally associated with BMI suggesting that motor milestone achievement and BMI are largely independent and that the delay in motor milestone achievement does not explain an increase in childhood overweight.

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CHAPTER 4

PARENTAL PHYSICAL ACTIVITY IS ASSOCIATED WITH OBJECTIVELY MEAUSURED PHYSICAL ACTIVITY IN YOUNG CHILDREN IN A SEX-SPECIFIC MANNER: THE GECKO DRENTHE COHORT

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ABSTRACT

Background

Physical activity (PA) is important in combating childhood obesity. Parents, and thus parental PA, could influence PA in young children. We examined whether the time spent at different intensities of PA and the type of parental PA are associated with the PA of children aged 4–7 years, and whether the associations between child-parent pairs were sex-specific.

Methods

All the participants were recruited from the Groningen Expert Center for Kids with Obesity (GECKO) birth cohort (babies born between 1 April 2006 and 1 April 2007 in Drenthe province, the Netherlands) and were aged 4–7 years during measurement. PA in children was measured using the ActiGraph GT3X (worn at least 3 days, ≥10 hours per day). PA in parents was assessed using the validated SQUASH questionnaire.

Results

Of the n=1,146 children with valid ActiGraph data and 838 mothers and 814 fathers with valid questionnaire data, 623 child-parent pairs with complete data were analysed. More leisure time PA in mothers was associated with more time spent in moderate-to-vigorous PA (MVPA) in children (Spearman r=0.079, p<0.05). Maternal PA was significantly related to PA in girls, but not boys. More time spent in maternal vigorous PA, in sports activity, and leisure time PA, were all related to higher MVPA in girls (Spearman r=0.159, r=0.133 and r=0.127 respectively, P_{all}<0.05). In fathers, PA levels were predominantly related to PA in sons. High MVPA in fathers was also related to high MVPA in sons (r=0.132, p<0.5). Spending more time in light PA was related to more sedentary time and less time in MVPA in sons.

Conclusion

Higher PA in mothers, for instance in leisure activities, is related to higher PA in daughters, and more active fathers are related to more active sons. To support PA in young children, interventions could focus on the PA of the parent of the same sex as the child. Special attention may be needed for families where the parents have sedentary jobs, as children from these families seem to adopt more sedentary behaviour.

INTRODUCTION

Overweight and obesity is a growing problem in children. According to the World Health Organization, more than 42 million children aged under five were estimated to be overweight worldwide in 2013[1], an increase from 4.2% of the overall population in 1990 to 6.7% in 2010. This prevalence is expected to be 9.1% in 2020[2]. Compared to normal-weight children, overweight or obese children are four times as likely to be overweight in adulthood, resulting in increased healthcare costs[3-5] and an increased risk of developing health problems such as diabetes, heart disease and certain cancers later in life[5,6].

Overweight and obesity are a consequence of a disturbed energy balance[7]. An important energy balance-related behaviour in addition to diet, is daily physical activity (PA)[8]. A lack of habitual exercise and PA in young children are related to higher body mass index (BMI)[9], greater skinfold thickness[9,10], greater fat mass[11] and obesity status[12-14]. To prevent future overweight in children, the determinants of their PA levels should be considered by looking at all aspects of their ecological system, including any obesogenic conditions. The ecological system closest to a child is the microsystem, which includes family, peers, school, health services and religious groups[15], with parents as important socializing agents[16]. Parents strongly determine the social and physical environment of their young children[17]. This influence may also provide an important link between the parents' PA level and their children's[18]. Parents influence their children's PA by providing modelling support (being physically active themselves) and social support (praising the child, watching the child participate in PA, engaging in parent–child co-activity, transporting their children to places where they can be active, and parental encouragement)[19,20].

Numerous studies have examined the relationship between parenting styles or parental support and children's PA[21-23]. Several studies have focused on the specific relationship between PA levels in parents and the PA levels of their children. One review found little evidence to support the hypothesis that higher PA levels in parents are associated with higher PA levels in children[24]. Another review showed a mixed pattern of associations between the PA levels of parents and those of their children. Six of the studies that were included confirmed an association, while seven studies found a weak or no association[23]. These mixed findings might be due to heterogeneity in study designs with regard to the number and age ranges of participants, geographical location and the methods used to assess PA.

Assessing PA is particularly difficult in young children. Their activity patterns are less structured than the PA habits of adults, and characterized by relatively short bouts of spontaneous, intense PA[25,26]. This spontaneous behaviour in children is difficult to summarize and report by observation, so questionnaires or parental reports are prone to measurement error[27]. Objective measurements, for example with tri-axial accelerometers, are likely to capture all movements[28,29]. Accordingly, the use of tri-axial accelerometry to obtain more valid and precise measurements of children's PA might better identify the associations between the PA levels of parents and their children.

The aim of this study was to examine whether the time spent at different intensities of PA and the type of parental PA are associated with objectively measured daily PA of their 4 to 7-year old offspring. Since other studies previously found that the relationship between the PA of parents and their children depended on sex[30,31], we specifically analysed the associations in child-parent pairs: mothers and daughters, mothers and sons, fathers and sons, and fathers and daughters. We hypothesized that children with more active parents are more physically active, compared to children with less active parents.

METHODS

Participants

All children aged between 4 and 7 years, (mean age 6.1 ± 0.5 years) participating in the GECKO Drenthe birth cohort were included in the study. The GECKO Drenthe study is a population-based birth cohort studying early risk factors for overweight and obesity in children living in Drenthe, a northern province of the Netherlands. Parents and their babies born between 1 April 2006 and 1 April 2007 in Drenthe were recruited for the study. Details of the study design, recruitment and study procedures are described in detail elsewhere[32]. At baseline, the parents of 2,997 children consented to participate, 2,874 of whom actively participated in the study. Data were collected from the last trimester of pregnancy onwards by midwives and gynaecologists, and after birth during regular check-up visits to the Well Baby Clinics and municipal health services as part of the nationwide Youth Health Care programme which monitors the health, growth and development of children from birth to 18 years. Height and weight were measured by trained youth healthcare nurses at age six years during a regular check-up. The overweight and obesity of children was classified according to the cut-offs of Cole *et al*.[33]. Socioeconomic status (SES) was assessed by the education level of the parents (low/middle education or higher vocational education) and the highest household income, both registered during pregnancy. The height and weight of the parents were self-reported in questionnaires. Adult overweight was defined as BMI between 25 and 29.9 kg/m^2 and obesity as ≥30 kg/m^2. Written informed consent was obtained from parents and this study was approved by the Medical Ethics Committee of the University Medical Center Groningen in accordance to the 1975 Declaration of Helsinki, as amended in 1983.

Physical activity

Between 2009 and 2013, families were contacted individually by research assistants to obtain data from parents and children simultaneously. PA in children was assessed using the ActiGraph GT3X (ActiGraph, Pensacola, FL) since the validity for measuring PA by questionnaire is low for children[34]. The ActiGraph is a reliable and valid device for measuring PA duration (minutes/day) at a certain intensity (sedentary behaviour (SB)), light PA (LPA), moderate PA (MPA), vigorous PA (VPA) and moderate-to-vigorous PA (MVPA) in young children[35,36]. The correlations between observed and ActiGraph intensity categorizations in young children ranged from 0.46 to 0.70 ($p<0.001$)[35]. The ActiGraph device was worn by the child with an elastic belt. Parents were instructed to let their child wear the ActiGraph on the iliac crest on the right hip for four consecutive days, including at least one weekend day, during all waking hours except when bathing or swimming[37,38]. To be included in the analysis for this study, the accelerometer had to be worn for at least 600 minutes/day for at least three days, regardless whether these were week or weekend days. Non-wearing time of the ActiGraph was defined as a minimum period of 90 minutes without any observed counts[39]. The cut-off points recommended by Butte *et al*. were used to calculate the time spent sedentary and in light PA (LPA) (240 counts per minute), LPA and moderate PA (MPA) (2120 counts per minute), and MPA and vigorous PA (VPA) (4450 counts per minute)[40]. The data collected were analysed in 15-second epochs[41]. Data were collected at a frequency of 30 Hz[42]. All the measurements for children with wearing times ≥840 min/day (14 h/day) were checked manually for sleeping time. Adherence to the Dutch PA guideline was defined in this study as ≥60 minutes of moderate to vigorous PA (MVPA) per day.

Parental PA was assessed by the validated SQUASH (Short QUestionnaire to ASsess Health enhancing physical activity)[43] questionnaire, as self-reporting remains the most feasible and commonly used method for collecting data in large populations[44]. Overall reproducibility of the SQUASH is 0.58 (95%-CI; 0.36–0.74). High-intensity activities are more reliable than low-intensity activities[43]. The SQUASH registers habitual physical activities and is pre-structured into four main domains: 1) commuting activities; 2) activities at work or school; 3) household activities and 4) leisure time activities (including sports). Parents reported the time spent in each domain using three main queries: number of days in the preceding week, average time per day (in minutes) and intensity in three categories (light/slow, moderate or intense/fast). For PA at work, parents reported the number of hours in light and moderate PA (seated and standing work, such as office work) and the number of hours in vigorous PA (such as carrying heavy loads). The total PA in minutes per week was calculated and the outcomes were classified as time spent in light, moderate and vigorous PA, as well as the time spent in different types of PA, which were commuting, leisure time, sports, household tasks, and time spent in physical activities at work or school, according to Wendel-Vos *et al*.[43] The SQUASH questionnaire classifies a mixture of sedentary and light activities such as 'office work' under 'light physical activity' (LPA). Implausible values which were excluded were: 1) PA≥18 hours/day; 2) separate categories exceeding plausible values on that particular category and 3) missing data for more than two questionnaire categories. Data for household activities were not analysed because they showed too much variation and were therefor considered less reliable[40]. Activities at work are conducted without children around and therefore no meaningful associations can be expected. The data cleaning was recorded and audited by a second investigator. If the investigators were unable to reach a consensus, a third researcher was consulted. Children were included in the present data analysis if valid PA data for the child and at least one parent were available (n=623, Fig. 1). Participants were excluded from the analysis for various reasons: withdrawal of informed consent, completion of informed consent form but failure to participate in the study, failure to participate at follow up (no contact details for PA assessment due to moving to another province/country), unwillingness to participate in PA measurement, or logistical problems in the distribution of the questionnaires or ActiGraphs.

Statistics

The data are presented as means with standard deviations, as rates in N and percentages, or if the data were skewed, as the median of the 25th and 75th percentiles. As most PA variables were more or less skewed, Spearman correlations were used to assess the associations between parental and child PA at different intensities. Since parental influence can be modified by education level, and both parental and child activities may be influenced by income level, education and income were investigated as potential modifiers in linear regression models. Dependent skewed variables were ln-transformed for linear regression. For reasons of clarity, only SQUASH results for sports, leisure time and active commuting are presented in Tables 2 and 3 alongside total PA (TPA), LPA, MPA, VPA and MVPA. The influence of gender was investigated by stratification. Finally, analysis was conducted to establish whether the children in families with two active parents were more active than children in families with inactive parents. For this, the parents were stratified into gender-specific tertiles based on MVPA and then regrouped into three categories: two active parents (both highest tertile), two inactive parents (both lowest tertile) and all other combinations. Statistical analyses were performed using IBM SPSS Statistics 22 for Windows (SPSS Inc., Chicago, IL). The graphs were prepared using GraphPad Prism 5.04 (GraphPad Software Inc., USA).

RESULTS

The parents of 2,276 children were contacted and PA measurements of 1,475 children, 838 mothers and 814 fathers were collected. As shown in Figure 1, we obtained valid ActiGraph data from 623 children and PA data from at least one of their parents. Data from both parents were available for 606 of these children. The children were aged between 4.7 and 7.4 years (5.3-6.4, 5^{th}-95^{th} percentile). Age and BMI were comparable for boys and girls, and the boys were more active than the girls. The boys on average spent sixteen minutes per day more in MVPA ($p<0.001$) and as a result more often satisfied the Dutch norm for healthy PA in children (Table 1). The total PA (TPA) data of the children included in the analyses were comparable to data of the children who were excluded for lack of parental data. The TPA data for the parents with child PA data were also comparable to the TPA for the parents without valid child PA data (data not shown).

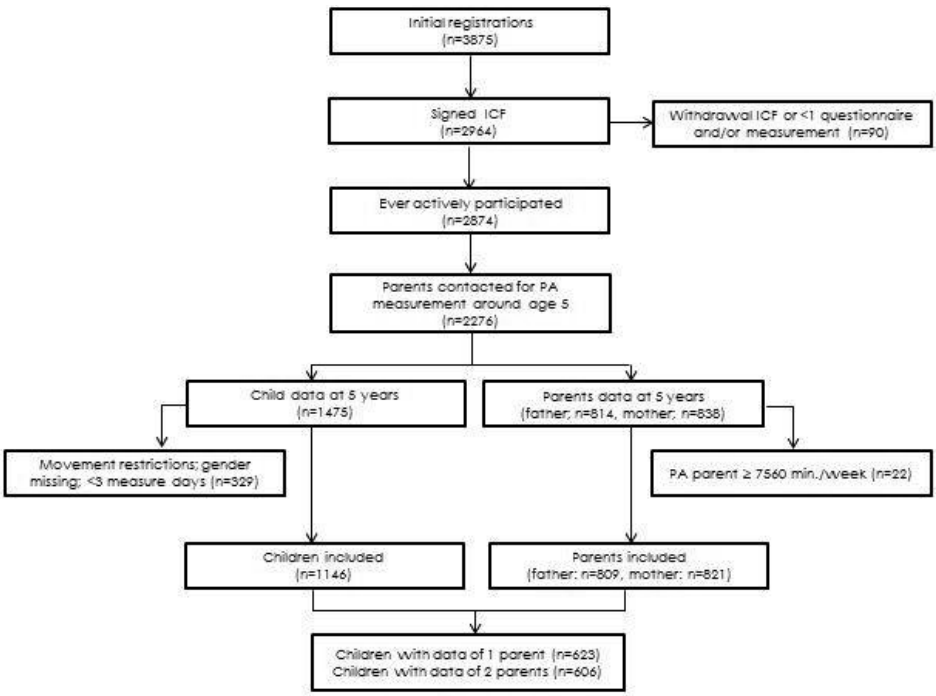

Figure 1 Flowchart of the participants

All participants were recruited from the GECKO Drenthe birth cohort (babies born between 1 April 2006 and 1 April 2007 in Drenthe, the Netherlands) and measured for PA between 2009 and 2012 when aged 4–7 years.

Table 1 Descriptive characteristics of children and parents in the GECKO Drenthe cohort

Child factors	N	Girls	N	Boys	P-value
Age at PA measurement (years)	299	6.1 ± 0.5	324	6.1 ± 0.5	0.93
Ethnicity (%)	282		304		0.32
Dutch		94.7		96.4	
Non-Dutch		5.3		3.6	
Highest household income, N (%)	267		279		0.22
≤EUR1150		11 (4)		6 (2)	
EUR1151–3050		179 (67)		173 (62)	
EUR3051–3500		51 (19)		69 (25)	
≥EUR3501		26 (10)		31 (11)	
BMI (kg/m²)	262	16.0 ± 1.5	277	16.0 ± 1.2	0.57
Physical activity (PA)	299		324		
Total PA (counts/minute, cpm)		764 ± 197		839 ± 241[a]	**<0.001**
Sedentary (hrs/day)		6.41 ± 0.92		6.27 ± 0.96	0.053
Light PA (hrs/day)		4.28 ± 0.61		4.31 ± 0.62	0.58
Moderate PA (min./day)		40 (31; 48)		48 (40; 61)[a]	**<0.001**
Vigorous PA (min./day)		16 (11; 24)		20 (14; 28)	**<0.001**
Moderate-to-vigorous PA (min./day)		55 (43; 72)		71 (54; 90)	**<0.001**
Adherent to PA guideline, N (%)		132 (44)		215 (66)	**<0.001**
Parent factors	**N**	**Mothers** (n=621)	**N**	**Fathers** (n=608)	
Age (years)	620	37.1 ± 4.4	579	40.0 ± 5.0	
BMI at PA measurement (kg/m²)	417	24.6 ± 4.0	372	25.4 ± 3.1	
Overweight and obesity, N (%)	417	164 (39.3)	372	178 (48.0)	
Education level (%)	595		578		
Low/middle		348 (58.5)		378 (65.4)	
High (higher vocational)		247 (41.5)		200 (34.6)	
Physical activity (PA)	621		608		
Total PA (hrs/day)		8.0 (6.3–10.3)		7.9 (6.6–9.4)	
Light PA (hrs/day)		6.5 (4.7–8.4)		6.0 (2.7–7.4)	
Moderate PA (hrs/day)		1.14 (0.57–2.50)		0.93 (0.29–4.14)	
Vigorous PA (hrs/day)		0.00 (0.00–0.26)		0.14 (0.00–0.43)	
Moderate-to-vigorous VPA (hrs/day)		1.29 (0.71–2.77)		1.32 (0.57–4.56)	
Sports (hrs/day)		0.14 (0.00–0.36)		0.14 (0.00–0.43)	
Leisure time PA (hrs/day)		0.79 (0.43–1.38)		0.89 (0.50–1.53)	
Housework (hrs/day)		3.57 (2.29–6.00)		1.00 (0.29–2.00)	
Active commuting (hrs/day)		0.00 (0.00–0.10)		0.00 (0.00–0.07)	
Active work (hrs/day)		3.43 (2.14–3.86)		5.71 (4.57–6.07)	

All the participants were recruited from the GECKO Drenthe birth cohort (babies born between 1 April 2006 and 1 April 2007 in Drenthe, the Netherlands). The data are presented as means ± standard deviations or as medians of the 25th and 75th percentiles or as percentages.

Table 2 shows the associations between parental and child PA. Generally, the parents' total PA was not associated with the PA levels of their offspring. No clear associations could be found between the intensities of the parent's PA and their children's. Only more time in light PA for fathers was associated with lover levels of MPA in children. With respect to the type of activities, we found that the children of mothers with higher leisure time PA had higher MVPA levels and less sedentary time. This sedentary behaviour in children was also related to more sports activity in mothers, but also to more active commuting time in mothers.

Table 2 Spearman's correlations between the PA of the mothers and fathers and their children

	All children					
	TPA	**SB**	**LPA**	**MPA**	**VPA**	**MVPA**
Physical activity (PA) Mother						
Total PA	0.018	-0.013	0.023	0.016	0.030	0.020
Light PA	0.003	0.024	0.004	-0.023	0.003	-0.020
Moderate PA	0.000	-0.070	0.042	0.041	0.007	0.035
Vigorous PA	0.047	-0.038	0.004	0.072	0.068	0.072
Moderate-to-vigorous PA	0.019	-0.076	0.044	0.062	0.020	0.052
Sports	0.040	**-0.083***	0.070	0.058	0.066	0.064
Leisure time PA	0.052	**-0.082***	0.067	0.073	0.065	**0.079***
Active commuting	-0.050	**0.085***	-0.032	-0.048	-0.011	-0.030
Physical activity (PA) Father						
Total PA	0.010	0.013	0.078	-0.046	0.010	-0.022
Light PA	-0.032	0.051	0.025	**-0.098***	-0.031	-0.079
Moderate PA	0.027	-0.021	0.011	0.030	0.011	0.030
Vigorous PA	0.024	-0.014	0.038	0.066	0.056	0.064
Moderate-to-vigorous PA	0.041	-0.028	0.019	0.056	0.035	0.056
Sports	-0.010	0.000	0.000	0.041	0.049	0.040
Leisure time PA	-0.002	-0.039	0.080	-0.021	0.015	0.001
Active commuting	-0.034	0.064	-0.024	-0.040	-0.038	-0.040

All the participants were recruited from the GECKO Drenthe birth cohort (babies born between 1 April 2006 and 1 April 2007 in Drenthe, the Netherlands) and measured for PA between 2009 and 2012 when aged 4–7 years. ***** *$p<0.05$, values indicate Spearman's rho. TPA = total physical activity; SB = sedentary behaviour; LPA = light physical activity; MPA = moderate physical activity; VPA = vigorous physical activity; MVPA = moderate and vigorous physical activity.*

Table 3 presents the specific parent-child pair correlations. No associations were found regarding total PA. Regarding the time spent in PA of different intensities, higher levels of MPA, VPA or MVPA in parents were generally related to higher levels of MVPA in sons or daughters. More specifically, higher VPA in both mothers and fathers was related to higher MVPA in daughters, whereas for sons, only paternal MPA and MVPA were significantly associated with MVPA in sons. A higher level of VPA in mothers was also expressed in the association between more time in sports and leisure time PA in mothers and more MVPA in daughters. In contrast, higher levels of light PA in fathers correlated with lower levels of MVPA in sons, and reciprocally also with more time in sedentary behaviours in sons, but not in daughters. Comparing families with two active parents, families with one active parent and families with two inactive parents, no other associations were found for PA in children than those already described (data not shown).

Table 3 Spearman's correlations between the PA of the mothers and fathers stratified for sons and daughters.

	Sons		**Daughters**	
	SB	**MVPA**	**SB**	**MVPA**
Physical activity (PA) Mother				
TPA	-0.062	0.000	0.040	0.078
LPA	-0.027	-0.038	0.076	0.035
MPA	-0.055	0.034	-0.085	0.057
VPA	0.026	0.007	-0.051	**0.159***
MVPA	-0.070	0.047	-0.080	0.078
Sports	-0.072	-0.003	-0.091	**0.133***
Leisure time PA	-0.080	0.059	-0.084	**0.127***
Active commuting	0.037	-0.054	**0.146***	-0.016
Physical activity (PA) Father				
TPA	0.041	-0.092	-0.014	0.075
LPA	**0.122***	**-0.228****	-0.019	0.072
MPA	-0.079	**0.147***	0.038	-0.067
VPA	0.049	-0.027	-0.083	**0.141***
MVPA	-0.061	**0.132***	0.002	-0.003
Sports	0.069	-0.046	-0.073	0.103
Leisure time PA	-0.036	-0.002	-0.053	0.021
Active commuting	0.087	-0.080	0.045	-0.026

*All participants were recruited from the GECKO Drenthe birth cohort (babies born between 1 April 2006 and 1 April 2007 in Drenthe, the Netherlands) and measured for PA between 2009 and 2012 when aged 4–7 years. *p<0.05, **p<0.01, values indicate Spearman's rho. TPA = total physical activity; SB = sedentary behaviour; LPA = light physical activity; MPA = moderate physical activity; VPA = vigorous physical activity; MVPA = moderate and vigorous physical activity.*

We hypothesized that more active fathers would have more active children, and thus, that fathers with more time spent in light PA would have be positively association with more time spent in higher intensities of activity in children. A positive association between light PA of the father and sedentary time of the son was an unexpected finding. We subjected this latter finding to further study, and especially aimed to understand the nature of the light PA of the father. Part of the LPA in the SQUASH questionnaire come from work-related activities, including office work (sitting/standing work, walking now and then, or walking with light carrying activities). Since this type of work may be related to a higher socioeconomic position of the family, we studied the effects of family income and parental education level on the associations between parental PA and child PA. Parents' income and education levels were found not to influence the association between parental PA and child PA in general (data not shown), though the association between paternal LPA and a son's sedentary behaviour could be fully explained by the father's education level (Table 4).

No direct effect of income was found on the association between paternal LPA and sedentary time in sons (Model 2, Table 4). Still, fathers with a high level of LPA spent more time in occupational PA (5.3 against 6.1 hours for the lowest vs. highest LPA tertiles, $p<0.001$), which was mostly classified as light activity (office work and intermittent sedentary work) and they had a higher income (15% against 41% highest income for the lowest vs. highest LPA tertiles, $p=0.009$ for Chi^2 test).

Table 4 The association between paternal LPA and sedentary time in sons is explained by paternal education level.

		Std. B	β	95% CI (β)	P-value
Crude model for paternal LPA and sedentary time of sons					
	Paternal LPA (min/week)	0.144	0.164	0.027 – 0.301	0.019
Crude model for paternal education level and sedentary time of sons					
	Paternal education level	0.121	0.245	0.017–0.473	0.035
Adjusted models					
Model 1	Paternal LPA	0.100	0.113	-0.030–0.256	0.119
	Paternal education level	0.141	0.280	0.030–0.531	0.029
Model 2	Paternal LPA (min/week)	0.100	0.114	-0.030–0.257	0.119
	Paternal education level	0.137	0.272	0.0001–0.544	0.050
	Family income	0.011	0.014	0.160–0.188	0.873

Std. B, standardized β coefficient; 95% CI (β), 95% confidence interval of the β coefficient. Model 1 presents the mutually adjusted model for explaining sedentary time in sons using both LPA and the father's education level. Model 2 presents further adjustment of Model 1 by family income. Paternal LPA was ln-transformed to obtain a normal distribution of the residuals. The outcome 'sedentary time in sons' is used in hours/day and was normally distributed. For interpretation, a β of 0.245 for paternal education level means fifteen more minutes per day (0.245 hours) of sedentary behaviour for the sons of high and low educated fathers.

DISCUSSION

This study found that mothers who spent more time in VPA and more time in sports and leisure time PA had daughters who spent more time in MVPA, whereas fathers with higher levels of MPA and MVPA had sons with higher levels of MVPA. These findings support the hypothesis that higher levels of more intense PA in parents are associated with higher levels of more intense PA in children, and support a modelling role of parents in the PA levels of their children that is sex-specific. Furthermore, higher levels of active commuting in mothers were associated with more sedentary time in daughters, and higher levels of LPA in fathers were associated with more sedentary time in sons. This latter association could be fully explained by the education level of the fathers, suggesting that children from families where the parents have sedentary jobs seem to adopt more sedentary behaviour, as well.

Although many studies have been published on the association between parental PA and child PA, few used objective measurements (e.g. accelerometry) to assess activity levels in pre-schoolers and distinguished the gender-specific relationships between parental PA and child PA as well. Some studies used accelerometry only in children[45-48] and two studies also used accelerometry in parents[49,50]. Most previous studies support the idea that the PA level of parents is associated with the PA of preschoolers[45,49-51]. Two studies showed no clear association with parental PA, which could be explained by their use of self-reported PA rather than objectively measured PA, or differences in socioeconomic status[46,47]. Additionally, in 431 children of 10-12 years old, Jago *et al*. did not find an association between PA in parents and children, despite the use of accelerometry for both[52]. The contradictory results in that study could be explained by the children's higher age, since research focusing on age-related social influences found that associations with PA in adolescents shift from parents to peers[53]. A more recent study by Jago *et al*. in 1,267 five- and six-year-olds showed a weak association between the MVPA of children and their parents[51]. Both the children's and the parents' PA in that study were measured using accelerometry. Other PA intensities were not reported.

Overall, we found differences between the role of the mothers' and the fathers' PA on their children's PA. Considering boys and girls together, maternal PA was more often and more significantly associated with PA and sedentary behaviour, compared to paternal PA. Previously, Taylor *et al.* showed that paternal PA was more predictive of child activity than maternal PA[49]. Sallis *et al.* only studied the role of maternal PA on children's PA, and not paternal PA, and found no association[46]. Our previous study of the GECKO Drenthe cohort at toddler age (3-4 years) found that maternal active commuting was associated with lower BMI and higher levels of light physical activity in children[54]. This could be explained by the mothers' active participation in daily PA with their children, contributing to healthier BMI in their children.

Active fathers had active sons. This positive correlation between fathers' and sons' PA was observed previously[51] and was also found in a review of 150 mostly cross-sectional studies with subjective measurement of PA, i.e. questionnaires or observation[55]. Recently, Vollmer *et al*. also found a positive correlation between the VPA of 150 fathers and the VPA of their 3 to 5-year-old children in one-on-one interviews[56]. In addition, and more unexpectedly, we found that paternal LPA had a significant positive correlation with sedentary time and an inverse association with the MVPA of boys. Considering the determinants of paternal LPA in our study, this included time spent at work ($r=0.23$, $p<0.001$). Accordingly, doing seated office work was counted as time spent in LPA, while it was actually time spent in sedentary time. Here, low paternal LPA was correlated with lower offspring sedentary time. Father-child associations using objectively measured sedentary time show mixed findings[52,57,58]. Fathers with lower LPA in our study were younger, had lower incomes and education levels, did less housework and had higher BMI (data not presented). Although children with higher income parents are presumed to have healthier lifestyles[59], fathers and sons with lower SES may not necessarily be less active because SES is unrelated to PA in pre-schoolers and school-aged children[60] but is related to sedentary time[52]. This difference in the attribution of determinants for PA and sedentary behaviour could explain why the association between lower LPA in fathers and lower levels of sedentary time in boys ceased to be significant when controlling for education level. In general, it is important that determinants for PA and sedentary behaviour are different and therefore the mechanism by which higher and lower levels of PA and sedentary behaviour are determined are different. The fathers in our study with low LPA may have had lower SES, and also different interactions with their boys than the older, lower BMI, more highly educated and higher income fathers. The father's type of work, the time available for children, the money available for sports or video gaming equipment and television viewing, the neighbourhood where the child grows up, and the father's knowledge of health behaviour are all factors which could affect the association between the activity levels of fathers and boys.

The representativeness of the study population, its large sample size and the objective measurement of PA in children are all important strengths of this study. This study included 623 parent/child combinations, which is more than other studies of young children (n=33 to n=347)[45-47,49,50]. The selection bias was weak, since parents were not recruited specifically for a PA study, but recruited from among the participants in the birth cohort[32]. In addition, no differences were found between the PA levels of children for whom parental data was or was not recorded. The number of children who met the Dutch activity norm for a healthy lifestyle was 44% for girls and 66% for boys, which corresponds reasonably well with the national average of 50% in children aged 4-11 years between 2006 and 2012[61]. The PA in children was objectively measured, which is more accurate than PA measured by questionnaires[19].

Conclusion

Mothers who spent more time in vigorous PA, for instance in sports or leisure time activities, had more active daughters. Fathers who spent more time in moderate intensity PA had more active sons. The intensity of the parents' physical activity seemed to be particularly related to the time spent in moderate intensity activity in children, but not to sedentary time. Sedentary activities of children may be dependent on other family-related factors such as the parents' occupational characteristics. To encourage PA in young children, interventions could focus on the PA of parents, taking into account that especially fathers influence their sons and mothers their daughters. Further research is warranted into the parents' occupational factors, as children seem to adopt more sedentary habits in families where the parents have sedentary work.

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CHAPTER 5

THE ROLE OF FITNESS IN THE ASSOCIATION BETWEEN FATNESS AND CARDIOMETABOLIC RISK FROM CHILDHOOD TO ADOLESCENCE

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ABSTRACT

Background

Fatness and fitness both influence cardiometabolic risk. Objective The purpose of this study was to investigate whether childhood fatness and increasing fatness from childhood to adolescence are associated with cardiometabolic risk during adolescence and how fitness affects this association.

Methods

Of 565 adolescents (283 boys and 282 girls) from the TRacking Adolescents Individual Life Survey (TRAILS) data on anthropometric parameters (age 11 and 16), metabolic parameters and fitness (age 16) were available. BMI and skinfolds were used as measures for fatness. Increasing fatness was calculated by subtracting Z-scores for fatness at age 11 from Z-score fatness at age 16. Cardiometabolic risk was calculated as the average of the standardized means of mean arterial pressure, fasting serum triglycerides, HDL-cholesterol, glucose, and waist circumference. Insulin resistance was calculated by HOMA-IR. Fitness was estimated as maximal oxygen consumption (VO_2max) during a shuttle run test.

Results

Boys showed a higher clustered cardiometabolic risk when compared to girls ($P<0.01$). Childhood fatness (age 11) and increasing fatness were independently associated with cardiometabolic risk during adolescence. In boys, high fitness was related to a reduced effect of increasing fatness on clustered cardiometabolic risk. Childhood fatness, increasing fatness and fitness were independently associated with HOMA-IR. Moreover, in boys this association was dependent of fatness.

Conclusion

Childhood fatness and increasing fatness are associated with increased cardiometabolic risk and HOMA-IR during adolescence, but a good fitness attenuates this association especially in fat boys

INTRODUCTION

According to the World Health Organization, 4.9%-22.5% of European boys is overweight and 2.4%-10.3% is obese. In girls overweight ranges from 6.9%-19.9% and obesity from 2.0%-12.3%[1]. In children overweight is of clinical interest because of its association with metabolic risk factors for cardiovascular disease, such as hyperlipidemia, hypertension[2,3] hyperglycemia and insulin resistance[4]. Studies on tracking overweight report an increased risk of overweight and obese youth becoming overweight adults[5] and therefore childhood overweight has most significant long-term consequences[6].

In adults, several studies show that higher cardio respiratory fitness attenuates cardiometabolic risk[7,8]. Especially among those with obesity, fitness attenuates cardiometabolic risk. This finding generated the 'fat but fit' paradigm which states that fat but fit people have healthier cardiometabolic outcomes than fat but unfit people, and are sometimes even as healthy as unfit but not fat people. Also in children and adolescents, cross-sectional studies have reported that among children and adolescents with high fatness, high fitness is related to decreased cardiometabolic risk[9].

The influence of childhood fatness, and in particular the changes in fatness on cardiometabolic risk and how fitness effects this association has not been studied in depth. Therefore, the aim of this study was to investigate whether childhood fatness and increasing fatness from childhood to adolescence are associated with cardiometabolic risk during adolescence and how fitness affects this association.

METHODS

Subjects

Data was collected as part of the 'Tracking Adolescents Individual Lives Survey' (TRails)[10]. TRails is a prospective cohort study in healthy Dutch children who have been followed from age 11 into adolescence. TRAILS participants were selected from five municipalities in the North of the Netherlands. The present study involves data from the first (mean age 11.4 years, SD=0.56) and third (mean age 16.1 years, SD=0.5) examination which ran from March 2001 to July 2002 and from September 2005 to December 2007, respectively. The initial TRails population consisted a total of 2230 children. Biochemical data and fitness were only measured in the third examination. Because of financial and practical reasons, schools were selected at random to participate in the collection of biochemical measures and/or fitness test. For this study 1665 children were excluded because no data was available on biochemical measures or fitness measures or children suffered from physical complaints which interfered with measurement of fitness (knee injuries). The final sample size included five hundred and sixty-five children (283 boys and 282 girls). The study protocol was approved by the National Dutch Medical Ethics Committee on research involving human subjects. Written informed consent was obtained from the children and the children's parents or custodians.

Measures of fatness and associated metabolic factors

Height, weight, waist circumference and skinfolds were measured at school after removing shoes and heavy clothing. Weight was measured in kilograms using a calibrated analogue Seca balance scale (Model 770; Hamburg, Germany). Height was measured in centimetres using a Seca stadiometer (Model 214; Hamburg, Germany). Waist circumference was measured in centimetres taken midway between the lowest rib and the iliac crest. Four skinfolds (triceps, biceps, subscapular and suprailiac) were measured by trained study personnel using standardized protocols and calibrated equipment, i.e. a Harpenden skinfold caliper (CMS instruments, London, UK). Glucose, insulin, triglycerides, TC, and HDL-C were determined from a fasting blood sample according to standard laboratory procedures. LDL-C was calculated according to Friedwald's equation[11]. Insulin resistance was calculated as HOMA-insulin resistance (HOMA-IR) using the following equation: ([insulin] * [glucose])/22.5[12].

Resting diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured using Dinamap Critikon® 1846SX (Critikon® inc., Tampa, FL, USA) on the right arm in a horizontal resting position. Mean arterial pressure (MAP) was calculated as: DBP + (1/3 * (SBP - DBP)).

Clustered cardiometabolic risk score

A continuous variable was calculated for the clustered cardiometabolic risk. Waist circumference, fasting glucose, triglycerides, MAP and HDL-C were transformed into Z-score and added. The metabolic risk score was calculated as the sum for the 5 Z-scores divided by 5. Thereby triglycerides were ln-transformed to obtain a normal distribution and HDL-C was inverted. In the same manner a clustered metabolic Z-score was obtained with the exclusion of waist circumference.

Cardio respiratory fitness

A 20-m shuttle run test (SRT) was used as an objective and validated measurement to assess fitness[13]. Participants had to run back and forth on a 20m course and pivot on the 20m line, while keeping the pace with audio signals emitted from a pre-recorded compact disc. The initial speed was 8 km/h and the speed increased by 0.5 km/h every minute. In a subsample of 272 (48.1%) participants, heart rate (HR) monitoring was performed using Polar Team System series 1 (Polar, Kempele, Finland). In this group, an extra criterion for maximum exertion was applied as a heart rate above 185 beats/minute. Performance on the test, measured by VO_2max, did not differ between participants wearing a HR monitor and participants who did not (respectively 46.3±7.4 $ml^{-1}*min^{-1}*kg$, 46.3±6.8 $ml^{-1}*min^{-1}*kg$; p=0.212). The estimated VO_2max was calculated using the following equation: $VO_2max = 31.025 + (3.238 * Speed) - (3.248 * Age) + 0.1536 * (Speed * Age)$[14].

Pubertal stage

The stage of pubertal development at age 11 years was assessed by parent ratings using schematic drawings of secondary sex characteristics associated with the five Tanner stages[15]. At age 16 years the Pubertal Development Scale (PDS) questionnaire[16] was used to assess pubertal development filled in by the adolescents themselves. The PDS questionnaire was recoded into 5 stages comparable to the Tanner stages[17].

Statistics

Data were analysed using SPSS 18.0. Boys and girls were analysed separately due to complex interactions between pubertal stage, fatness, CRF and cardiometabolic risk that were related to gender differences. Triglycerides, insulin, and HOMA-IR were Ln transformed because of lack of normality. A two-tailed Student's t-test was used to test for gender differences or Fisher exact test in case of categorical data. Increasing fatness was calculated by subtracting Z-scores for fatness (BMI and skinfolds) at age 11 from Z-score fatness at age 16. The associations between childhood fatness, increasing fatness and fitness and cardiometabolic outcomes during adolescence were studied by Pearson correlations. Regression analysis was performed to identify the independent contribution of fatness, increasing fatness and fitness to the clustered cardiometabolic risk score and HOMA-IR. Children were categorized into 4 groups based on the increasing fatness. Two groups were created for children with negative scores (ΔBMI 1<-1 and ΔBMI 2 between -1 and 0), which means that those children gained least weight; two groups were created for children with positive scores (ΔBMI 4>1 and ΔBMI 3 between 0 and 1), which means that those children gained most weight. In Model 1, we evaluated the association between childhood fatness (age 11) and the clustered cardiometabolic risk score in adolescence, adjusted for age, study location, Tanner stage (age 11) and pubertal development stage (age 16).

In Model 2, increasing fatness was added to test its relation with the clustered cardiometabolic risk score. In Model 3, fitness was added to evaluate its contribution independent of fatness and increasing fatness. In the final Model, Model 4, an interaction between fitness and increasing fatness was added. Missing data were replaced with the series mean if missings were less than 1%. Missing data for skinfolds at age 11 (6.4% for triceps, subscapular and suprailiacal; 23% for biceps) were replaced by imputation using available relevant variables (gender, age, weight at age 11 and age 16, height age 11 and age 16, other skinfolds at age 16). Missing data for PDS (9.6%) were replaced by multiple imputation using available relevant variables (gender, age, Tanner stage (age 11)) and anthropometric and biochemical measures.

RESULTS

Gender differences

In boys 11.8% were overweight at age 11 and 10.6% of the boys were overweight at age 16. In girls, 10.6% were overweight at age 11 and 10% of the girls were overweight at age 16 according to the international accepted definition[18]. Table 1 shows that at the age of 11 boys and girls did not differ regarding BMI, whereas the sum of skinfolds was higher in girls compared to boys ($p=0.02$). At age 16, girls had higher BMI ($p=0.04$) and sum of skinfolds ($p<0.01$) compared to boys, whereas boys showed higher clustered cardiometabolic risk score when compared to girls ($p<0.01$). This was due to higher MAP ($p=0.01$), triglycerides ($p=0.02$), fasting glucose ($p<0.01$) and lower HLD-C ($p<0.01$). As expected, boys had higher fitness ($p<0.01$) compared to girls.

Childhood fatness, increasing fatness, VO_2max and cardiometabolic risk

Table 2 shows that in boys childhood fatness correlated to the clustered cardiometabolic risk with and without waist at age 16. In girls, childhood fatness was related to the clustered cardiometabolic risk at age 16, however, this was fully explained by a correlation with waist circumference. Increasing fatness was significantly correlated to the clustered cardiometabolic risk in both boys and in girls and several, but not all individual cardiometabolic risk factors at age 16. In boys and girls VO_2max correlated inversely with the clustered cardiometabolic risk, however, in girls this correlation was mainly explained by a correlation with waist circumference. Regression was used to study the associations between childhood fatness, increasing fatness, fitness and the interaction between increasing fatness and fitness to the clustered cardiometabolic risk with adjustments for age, study location, and pubertal stage. Data are presented in Table 3. Only Models using BMI as a measure for fatness are presented, because BMI showed stronger associations with metabolic outcomes compared to skinfolds. In boys as well as in girls childhood fatness predicted clustered cardiometabolic risk during adolescence (Model 1). Model 2 showed that independently from childhood fatness, increasing fatness between age 11 and 16 was associated with clustered cardiometabolic risk. Weight gain in ΔBMI 1, ΔBMI 2, ΔBMI 3 and ΔBMI 4 were respectively 13.6 kg±7.5kg, 19.6 kg±5.3kg, 26,0 kg±5.5kg, 31.4 kg±7.2kg. Model 3 shows that in boys, fitness was associated with clustered cardiometabolic risk independent of fatness and increasing fatness. In girls there was only a trend for this association. The interaction between increasing fatness and fitness (Model 4) was only significant in boys. When adding the interaction to the Model, the independent effect of fitness disappeared ($\beta=0.023$; 95% CI: -0.006, 0.053), whereas the influence of increasing fatness increased. This interaction in boys was only significant when using BMI as a measure for fatness and not when skinfolds were used as a measure for fatness ($\beta=-0.008$; 95% CI: -0.08, 0.003). After excluding waist from the clustered cardiometabolic risk the interaction was no longer significant ($\beta=0.000$; 95% CI: -0.014, 0.012). This interaction between fatness and fitness is graphically depicted in Figures 1A and 1B.

Table 1 Descriptive characteristics of Dutch adolescents in the TRAILS cohort.

	Boys (n=283)	Girls (n=282)	P-value
Age 11			
Age (in years)	11.1.5 ± 0.5	11.0 ± 0.6	0.06
BMI (kg/m^2)	17.6 ± 2.4	17.6 ± 2.4	0.92
Sum of skinfolds (cm)	38.8 ± 18.8	43.8 ± 18.3	0.02
Pubertal stage (%)	31.1, 65.0, 3.9, 0, 0	35.8, 41.5, 17.4, 5.0, 0.4	<0.01
Age 16			
Age (in years	16.1 ± 0.5	16.0 ± 0.5	0.25
BMI (kg/m^2)	20.7 ± 2.7	21.1 ± 2.5	0.04
Sum of skinfolds (cm)	38.3 ± 19.6	57.1 ± 17.0	<0.01
Pubertal stage (%)	0.7, 1.4, 33.2, 64.7, 0	0, 0, 3.5, 75.9, 20.6	<0.01
Waist circumference (cm)	74.4 ± 7.3	74.0 ± 6.5	0.37
DBP (mmHg)	59.7 ± 6.4	61.5 ± 6.9	0.01
SBP (mmHg)	121.4 ± 12.0	113.4 ± 10.2	<0.01
MAP (mmHg)	80.2 ± 6.9	78.8 ± 7.1	0.01
LDL-C (mmol/l)	2.16 ± 0.61	2.33 ± 0.61	0.01
HDL-C (mmol/l)	1.40 ± 0.29	1.54 ± 0.31	<0.01
Total-C (mmol/l)	3.62 ± 0.67	3.93 ± 0.68	<0.01
Triglycerides (mmol/l)	0.70 (0.530, 0.87)	0.61 (0.48, 0.88)	0.02
Glucose (mmol/l)	4.60 ± 0.42	4.48 ± 0.46	<0.01
Insulin (mU/l)	11.8 (8.6, 15.0)	12.25 (9.6, 16.0)	0.03
HOMA-IR	2.35 (1.66, 3.07)	2.48 (1.90, 3.15)	0.19
Clustered cardiometabolic risk	0.08 ± 0.57	-0.08 ± 0.50	<0.01
Clustered cardiometabolic risk without waist	0.09 ± 0.59	-0.09 ± 0.54	<0.01
VO_2max (ml^{-1}*min^{-1}*kg)	50.3 ± 6.4	42.3.0 ± 5.2	<0.01

Data are presented as means ± SD. Ln transformed data are presented as median (25th - 75th percentile). Tanner stage and pubertal stage are presented as % in phase 1-5 (respectively: pre pubertal, early pubertal, mid pubertal, late pubertal, post pubertal). Clustered cardiometabolic risk is presented as a Z-score with average = 0 and SD = 1. A two-tailed Student's t-test for independent samples was used to test for gender differences. Differences in categorical data were tested with the Fisher exact test.

Childhood fatness, increasing fatness, VO_2max and HOMA-IR

In boys, childhood fatness was related to insulin and HOMA-IR at age 16, whereas in girls increasing fatness was positively related to HOMA-IR (Table 2). VO_2max also correlated inversely with insulin and HOMA-IR. These correlations were moderate for boys (r=-0.314; r=-0.310 respectively) and small to moderate for girls (r=-0.180; r=-0.186 respectively). When adjusting for age, study location, and pubertal development, childhood fatness predicted HOMA-IR in boys (Model 1) but not in girls. Increasing fatness (Model 2) was associated with HOMA-IR independent of fatness (age 11) in girls but not in boys. Fitness (Model 3) was associated with HOMA-IR independent of fatness and increasing fatness in both boys and girls. Only in boys there was a significant interaction between increasing fatness and fitness (Model 4). As in the clustered cardiometabolic risk, when adding the interaction to the Model, the independent effect of fitness disappeared (β=0.008; 95% CI: -0.22, 0.038). Furthermore, the effect of increasing fatness increased and became significant (β=0.592; 95% CI: 0.056, 1.129). Thus for boys the contribution of fitness to HOMA-IR depends on the growth in BMI between age 11 and age 16. The larger this growth the higher the contribution of fitness. This interaction between fatness and fitness is graphically depicted in Figures 2A and 2B.

Table 2 Correlations between BMI age 11, skinfolds age 11, increasing fatness, VO_2max and the metabolic risk factors at age 16.

Outcome measures (age 16)	**BMI (age 11)**		**Skinfolds (age 11)**		**ΔBMI (increasing fatness age 11 to age 16)^**		**ΔSkinfolds (increasing fatness age 11 to age 16)^**		**VO_2max (age 16)**	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Clustered cardiometabolic risk	0.476**	0.163**	0.466**	0.177**	0.193**	0.317**	0.205**	0.172**	-0.253**	-0.174**
Clustered cardiometabolic risk (without waist)	0.308**	-0.017	0.297**	0.025	0.094	0.219**	0.122*	0.094	-0.175**	-0.103
Waist circumference (cm)#	0.590**	0.471**	0.536**	0.414**	0.308**	0.343**	0.278**	0.245**	-0.289**	-0.229**
MAP (mmHg)#	0.171**	0.021	0.188**	-0.034	0.117*	0.009	0.096	0.049	-0.120*	0.065
DBP (mmHg)	0.026	-0.024	0.079	-0.050	0.067	0.004	0.060	0.062	-0.156**	0.071
SBP (mmHg)	0.292**	0.053	0.269**	-0.080	0.157**	0.126*	0.138*	0.134*	-0.026	0.061
Triglycerides (mmol/l)#	0.259**	-0.073	0.247**	-0.042	0.113	0.137*	0.173**	0.048	-0.119*	-0.086
HDL-C (mmol/l)#	-0.219**	-0.015	-0.103	-0.057	0.068	-0.189**	0.031	-0.072	0.007	0.159**
LDL-C (mmol/l)	0.171	0.015	0.218**	-0.041	0.149*	0.078	0.168**	0.082	-0.107	0.045
Total-C (mmol/l)	0.150*	0.020	0.217**	-0.047	0.154**	-0.010	0.162**	0.049	-0.086	0.089
Glucose (mmol/l)#	0.073	-0.006	0.155**	0.067	0.048	0.135*	0.035	0.031	-0.166**	-0.042
Insulin (mU/l)	0.207**	0.042	0.300**	0.026	0.052	0.161**	0.083	0.195**	-0.310**	-0.186**
HOMA-IR	0.204**	0.037	0.304**	0.039	0.056	0.180**	0.082	0.188**	-0.314**	-0.180**

*Data are Pearson correlation coefficients; *$p<0.05$; **$p<0.01$; ΔBMI: Z-score BMI age 16 -Z-score BMI age 11 #Factors of the clustered cardio metabolic risk; ^ Increasing fatness was calculated by subtracting Z-scores for fatness (BMI and skinfolds) at age 11 from Z-score fatness at age 16.*

Table 3 Associations between BMI, ΔBMI, VO2max, ΔBMI* VO2max and clustered cardiometabolic risk.

		Boys (n=283)			Girls (n=282)		
		Beta coefficient (95% CI)	**aR^2**	**R^2 change**	**Beta coefficient (95% CI)**	**aR^2**	**R^2 change**
Model 1	BMI (age 11)	0.107** (0.082, 0.132)	0.221	0.204	0.035* (0.010, 0.059)	0.106	0.017
Model 2	BMI (age 11)	0.130** (0.106, 0.155)	0.317	0.096	0.055** (0.032, 0.079)	0.215	0.119
	ΔBMI	0.263** (0.181, 0.345)			0.233** (0.160, 0.306)		
Model 3	BMI (age 11)	0.121** (0.096, 0.145)	0.338	0.021	0.051** (0.027, 0.075)	0.221	0.006
	ΔBMI	0.255** (0.175, 0.336)			0.225** (0.152, 0.299)		
	VO_2max	-0.014* (-0.023, -0.005)			-0.009 (-0.019, 0.001)		
Model 4	BMI (age 11)	0.117** (0.092, 0.141)	0.351	0.013	0.051** (0.027, 0.075)	0.219	0.000
	ΔBMI	0.948** (0.418, 1.477)			0.171** (-0.331, 0.673)		
	VO_2max	0.023 (-0.006, 0.053)			-0.013 (-0.046, 0.021)		
	ΔBMI* VO_2max	-0.015* (-0.026, -0.004)			0.001 (-0.011, 0.014)		

Model 1: + BMI age 11; Model 2: + ΔBMI; Model 3: + VO_2max; Model 4: + ΔBMI VO_2max. All Models were adjusted for age, study location, Tanner (age 11) and PDS (age 16); CI: Confidence interval; aR^2: adjusted R-square. ΔBMI: categorized differences in Z-score BMI age 11 and Z-score BMI age 16; Two groups were created for children with negative scores (<-1 and between -1 and 0), two groups were created for children with positive scores (>1 and between 0 and 1); Beta coefficients are unstandardised ; *p<0.05 ; **p<0.01.*

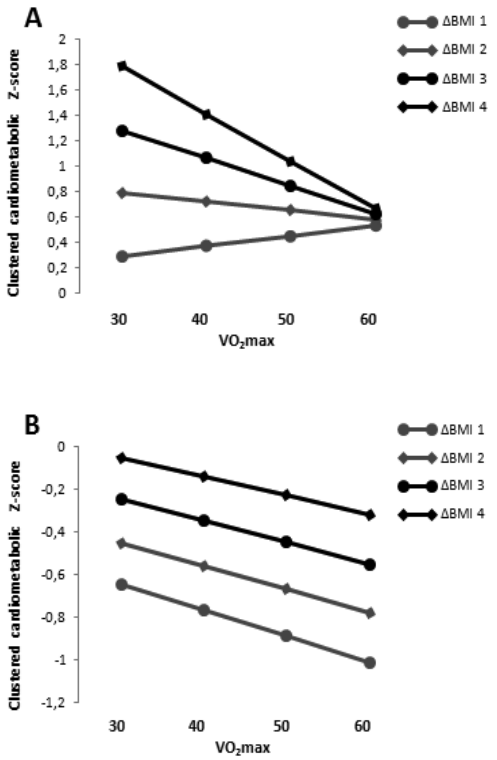

Figure 1 *Interaction between increasing fatness and fitness on cardiometabolic risk in (A) boys and (B) girls. Regression lines are presented for group 1 with lowest up to group 4 with highest increase in BMI Z-score. Regression coefficients as presented in Table 3a were used for the regression line. Studylocation, Tanner, PDS were kept constant.*

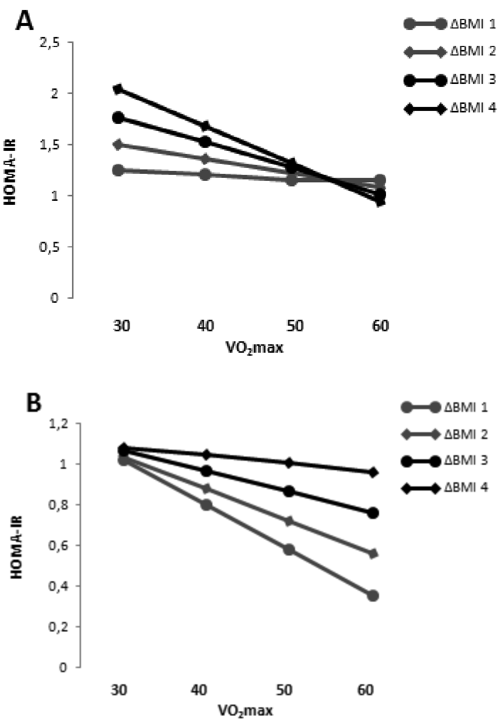

Figure 2 *Interaction between increasing fatness and fitness on HOMA-IR in (A) boys and (B) girls. Regression lines are presented for group 1 with lowest up to group 4 with highest increase in BMI Z-score. Regression coefficients as presented in Table 3 were used for the regression line. Studylocation, Tanner, PDS were kept constant.*

DISCUSSION

This study shows that childhood fatness and increasing fatness are independently associated with increased cardiometabolic risk and HOMA-IR during adolescence, and that good fitness attenuates this association especially in fat boys. In addition, in boys the effect of fitness on cardiometabolic risk and HOMA-IR depends on the increasing fatness. In girls fitness only influenced HOMA-IR but not the cardiometabolic risk independent of childhood fatness and increasing fatness.

In boys, measures of childhood fatness correlated to the clustered cardiometabolic risk either with or without waist circumference during adolescence. In girls, measures of childhood fatness were also correlated with the clustered cardiometabolic risk, however this was fully explained by a correlation with waist circumference. Associations between childhood fatness and individual cardiometabolic risk factors in later life were found before in a study of 31 obese children who were followed from the age of 13 till age 22[19]. Another study showed that the degree of fatness in childhood is tightly linked to adverse cardiometabolic outcomes in adulthood[20]. An interesting question that rises is whether there is an association between the initial degree of childhood fatness and later cardiometabolic risk or that childhood fatness is only relevant if it has tracked into later life. This study shows that, independent of the effects of childhood fatness, increasing fatness from childhood into adolescence is associated with clustered cardiometabolic risk and HOMA-IR during adolescence. A study with 186 obese adolescents who were followed for 19 months found that fatness was linked to individual cardiometabolic risk factors and changes in insulin sensitivity[21]. Cardiometabolic risk factors and changes in insulin sensitivity were assessed at baseline and after 19 ± 7 months. The cohort was stratified into three categories based on the 25th and 75th percentile of body mass index (BMI) z-score change. Subjects who reduced their BMI z-score significantly decreased their fasting and 2-h glucose levels and triglyceride levels and increased their high density lipoprotein cholesterol in comparison to subjects who increased their BMI z-score. BMI z-score changes negatively correlated with changes in insulin sensitivity ($r=-0.36$, $p<0.001$). Of 67 who had metabolic syndrome at baseline[22] (50%), most of whom decreased their BMI z-score, lost the diagnosis. However, these studies used clinical (obese) populations. TRails uses a general and not a clinical population. Therefore the finding of this study can be best compared with the findings of an Australian cohort study in which 172 children were followed from the age of 8 to 15 years[23]. They reported that children who were overweight or obese at 8 years of age were 7 times as likely to have cardiometabolic risk clustering in adolescence than were their peers who were not overweight or obese. They also reported that those with an increased waist circumference at age 8 years were 4 times more likely to have cardiometabolic risk clustering in adolescence than were children with a smaller waist circumference. It was concluded that association between measures of fatness in midchildhood and later adverse cardiometabolic risk is a result of the tracking of fatness status.

In line with other studies fitness was inversely related to the clustered cardiometabolic risk with or without waist circumference[24,25] and HOMA-IR[26]. In boys, fitness was associated with clustered cardiometabolic risk and HOMA-IR independent of childhood fatness and increasing fatness. In girls there was only an independent association with HOMA-IR but not with clustered cardiometabolic risk. This could be because of a lack of power or because of absence of more overweight or obese girls in the study population. Nevertheless, these findings are in line with cross-sectional studies[27] which studied the mediation of fitness on the association between fatness and cardiometabolic risk by stratification. Children and adolescents with 'high fatness and high fitness' have better cardiometabolic risk profiles than those classified as 'high fatness but low fitness'. However in these studies it is difficult to determine whether fitness modifies the association between fatness and cardiometabolic risk since fitness and fatness are heavily intertwined. Stratification by fatness does not always solve this problem because groups are not always equally balanced, resulting in lower average BMI in groups with 'fat but fit' children when compared to 'fat and unfit' children.

This study further shows that in boys there is a significant interaction between fitness and fatness which states that high fitness attenuates the association between fatness and clustered cardiometabolic risk especially in those who had higher increases in BMI between age 11 and age 16. For HOMA-IR, comparable results were found. One prospective study in which the association between fatness, fitness and cardiometabolic risk was studied was found. The Amsterdam Growth and Health Longitudinal Study followed 364 individuals (189 women) from adolescence (age 13) into adulthood (age 36) on fatness, fitness and cardiometabolic risk[28]. This study found independent influences of fatness and fitness on cardiometabolic risk. The associations between fitness and the metabolic syndrome decreased considerably when adjusted for fatness, but the associations remained statistically significant. The authors suggest that poor fitness may be associated with cardiometabolic risk partly because of its associations with body fatness[29] and also because of other mechanisms including insulin resistance[30], sub-clinical inflammation[31], or a common genetic background[32,33] that predisposes to low fitness and increased cardiometabolic risk.

Limitations and Advantages

This study shows some limitations while overweight girls were more often excluded due to missing data on fitness which might result in selection bias. In the current study puberty was assessed by using 2 different methods, one filled in by the parents (Tanner) at the first examination and second filled in by the adolescents (PDS) at the third examination. This might result into a less accurate definition of the maturity status, but does not influence the main outcomes. The advantage of this study is that it shows in a longitudinal design that childhood fatness, increasing fatness and fitness are independently associated with clustered metabolic risk and HOMA-IR. However, only fatness measures were tracked. In this study BMI as well as skinfolds were used as measures for fatness. Because BMI showed more obvious associations with the clustered cardiometabolic risk and HOMA-IR compared to skinfold, most of the time results from BMI are presented. This study used a valid measure of fitness and a subsample of participants (48%) was checked for maximal exhaustion rendering the measurements accurate.

To improve cardiometabolic risk in adolescents, interventions need to focus not solely on reducing fatness but also on physical activities that improve fitness.

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CHAPTER 6

GENERAL DISCUSSION

The aim of this thesis was to study how motor skill competence, physical activity (PA), cardiorespiratory fitness (CRF), weight status and cardiometabolic risk relate to each other during development from infancy to adolescence and to get insight in contextual factors influencing the development of motor skill competence, PA and weight status. The results presented in this thesis generally indicate that later achievement of motor milestones during infancy is linked to lower levels of PA during childhood. At the same time, this later achievement of motor milestones does not seem to be related to weight status during childhood. In adolescents, those with higher adiposity during childhood and with accelerated gain in body mass index (BMI) from childhood to adolescence can compensate for cardiometabolic risk with higher CRF. To stimulate PA, parents can act as role models since parental PA is related to childhood PA in a sex-linked manner. Stimulating CRF enhancing physical activities seems most relevant when improving cardiometabolic health. When studying health outcomes, a combination of different methods to measure PA and CRF is suggested.

Part 1. Relation between early motor development, physical activity, cardiorespiratory fitness, overweight and cardiometabolic risk

Infant motor skill competence and physical activity

From the literature it is not clear whether the association between infant motor skill competence and PA is reciprocal and how they influence each other over time. Wijtzes *et al.*[1] found a trend ($P<0.10$) between infants who achieved their motor milestones at an older age and lower levels of PA at age 2 years. We found evidence for an association between the age of reaching infant motor milestones to subsequent PA levels at age 5 years (**Chapter 2**). In brief, infants who achieved walking without support at an older age, but within the normal range of development, spent more time in sedentary behaviour and less time in moderate-to-vigorous PA (MVPA). Also in a large cohort of older children (N > 4400) of around 11-12 year of age, Mattocks *et al.*[2] found a weak association between better motor coordination at 6 months and higher subsequent PA. In addition, older age at achievement of motor milestones also predicted lower frequency of self-reported weekly sport participation in 14-year olds[3]. Thus, a better infant motor skill development may facilitate higher levels of PA in childhood, although the relationship may be reciprocal. This relation, albeit weak, is already visible during early childhood.

The differences in levels of childhood PA associated with infant motor milestone achievement are subtle. To illustrate, infants who reach their motor milestone 'walking without support' with 14 months, spend on average 30.8 minutes per week less in MVPA and 49 minutes per week more in sedentary time when aged 5 years compared to infants who reach their motor milestone 'walking without support' with 12 months (**Chapter 2**).

Reaching the moment of walking 2 month later was related to 56 minutes per week spent less in MVPA at an average age of 19 months in another study with infants[4]. It can be questioned how relevant these lower levels of MVPA and higher levels of sedentary time associated with later motor milestone achievement are. First, the lower levels of MVPA and higher amounts of time spent in sedentary behaviour (SB) associated with later achievement of motor milestones we found in our study are small but meaningful when compared to the effect of most interventions based on socio-ecological models. Interventions for stimulating PA in young children are reviewed by Ling *et al*.[5]. Most of these interventionsdo not find any effect on PA levels in preschoolers. From the 20 studies included in the review, just 3 studies found a higher levels of MVPA varying from 7 to 56 minutes per week; 3 studies found higher levels of total PA and 2 studies found lower levels of SB of 77 and 140 minutes per week. Since these interventions differed in setting, theoretical framework, parental involvement, PA measure and length of intervention, it is difficult to draw conclusions. Second, early motor skill competence might be relevant when considering the dynamic or synergistic role that motor skill competence plays in the initiation, maintenance, or decline of PA. The proposed conceptual model of Stodden *et al.*[6] describes a developmentally dynamic and reciprocal relationship between PA and motor skill competence in the way that decreased motor skill competence leads to lower levels of PA and lower levels of PA lead to decreased motor skill competence. Evidence for a reciprocal relationship between PA and motor skill competence was found from childhood to adolescence[7]. To our knowledge, no studies are published investigating the reciprocal relationship between PA and motor skill competence at younger ages. Based on evidence of Stodden's model it can be suggested that the associations between infant motor skill competence and subsequent PA might get stronger with increasing age. To illustrate this, if infants reach their motor milestones later, they have less opportunities to move around, explore and develop new skills. They will have lower levels of PA. Indeed we found that infants who reach their motor milestones later have lower levels of subsequent PA (**Chapter 2**). Because of these lower levels of PA, these children have less opportunities to develop new or more specified skills[8]. It can be assumed that the lower scores on motor skill competence in pre-schoolers and children during the last decennia[9,10] could be related to lower levels of PA. In addition, these lower levels of PA may partly be caused by later achievement of motor milestones. Pathway analysis are needed to test these reciprocal relations between motor skill competence and PA since both behaviours track during childhood[11]. Evidence from a longitudinal study in Finland showing that 'age at walking supported' and 'age at standing unaided' predicted sports participation at 14 years[3], and supports the idea of importance of better motor skill competence for future PA. Based on the outcomes of interventions promoting PA and the assumptions of

Stodden's model, the subtle association between infant motor skill competence and childhood PA is relevant, amongst other factors, when targeting childhood PA.

Infant motor skill competence and weight

Because it is unclear whether there is an association between motor skill competence and weight status and how the direction of this association is when studied prospectively, we studied weight before and after reaching motor milestones in the Dutch Twin Registry. Babies with lower birth weight (BW), although within the normal range, seem to reach their motor milestones later compared to those with a higher BW (**Chapter 3**)[12-15], even when adjusting for gestational age (GA). Associations found in our Dutch Twin Registry were in the same direction, although of larger magnitude, as in a Danish cohort with singletons, supporting that a lower BW is related to later motor milestone achievement in both twins and singletons. When studying the associations the other way around, motor milestone achievement and BMI later in childhood were largely independent of each other in our studies (**Chapter 2 and Chapter 3**) despite that motor milestone achievements was related to differences in PA levels. Although motor milestone achievement was related to overall adiposity at age 3 years in a small study of 47 infants[16] , our findings were more in line with a large Danish cohort of >25,000 infants. Based on the findings of our study and the large Danish study, we suggest that infants with lower BW achieve their motor milestones a little later compared to those with a higher BW and that infant motor milestone achievement is not likely to be associated with subsequent BMI during childhood.

Later motor milestone achievement

Although we concluded that motor milestone achievement and BMI during childhood were not likely to be related, we were interested in the possibility that there could be changes in the age of achieving motor milestones on a population level, that would explain changes in overweight over time. Indeed, we found that twins born in the earlier cohorts (e.g. from 1987-1989) achieved their motor milestones at an older age compared to twins born in the later cohorts (e.g. from 2005-2007) (**Chapter 3, Appendix 1**). The older age of achieving motor milestones was most pronounced in the age of standing and walking without support, but also visible in crawling. Babies born in 2005-2007 stand and walk without support almost one month later compared to babies born in 1987-1989. Although genetic variation seem to play a role in early motor skill competence[17], it is not likely that this has changed between 1987 and 2007. Several environmental factors influence infant motor skill competence as well. Infants who are not breastfed, consistently show lower scores on motor skill competence[18-22]. However, these effects might be influenced by socioeconomic status[23,24]. Also cultural differences exist. Like in several other studies[25-27] the Multicentre Growth Reference study Group from the World Health

Organization identified differences in achievement of motor milestones between infants of the countries Ghana, Norway, India, Oman, and USA[15]. Ghanaian infants showed the earliest onsets for sitting without support, standing with assistance, and walking with assistance when compared to more 'Westernized' countries. It was suggested that culture-specific care behaviours are the most likely contributing factor for these differences. Specifically in the Netherlands, we suggest that an important explanation for the older age of motor milestone achievement might be lack of 'tummy time'. Tummy time aids in developing neck, shoulder, and core strength which increases the development for other motor milestones[28]. To reduce the chance of sudden infant death syndrome, parents are recommended since 1987 to let their baby sleep on their back or side, instead of on their tummy. Since the increase in age of achieving milestones does seem to continue in a linear fashion with time, well beyond 1987, this may not be the only reason for later age of achieving motor milestones. This tummy time seems also thwarted by the arrival of equipment like maxi-cosies, babywalkers and screens like television and i-pads[29-32]. During development, infants should be encouraged to spent as much time as possible moving unrestricted, preferable in prone position, since this may contribute to higher levels of PA and a healthy growth pattern[4,33-36]. These higher levels in PA can be achieved through interventions focusing on motor skill competence in preschoolers (2-6 years)[37-39]. Based on this literature and the older age of motor milestone achievement we found in our study (**Chapter 3**) we suggest that environmental changes have resulted in changes in motor milestone achievement during the last decades.

Although infants achieve their motor milestones at an older age than two decades ago, this does not explain the population-wide increase in childhood overweight. The prevalence of overweight did increase in these two decades, but this was independent of the population shift in age of achieving motor milestones. This is in line with the findings from **Chapter 2**, that motor milestone achievement and BMI during childhood were not related. Thus, using **Chapter 2** and **3**, a direct pathway from motor skill competence to lower rates of overweight could not be confirmed.

Physical activity, cardiorespiratory fitness and health

In contrast to our expectations we did not find an association between PA and BMI or waist circumference during childhood (**Chapter 2**). Evidence from observational studies investigating dose-response relationships suggest that more PA is better for several health outcomes[40]. More specifically, PA is suggested to be protective against child and adolescent obesity in cross-sectional studies[41], although prospective studies show mixed findings[42-45]. Discrepancies between outcomes are suggested to come from studying different age groups, the use of different methods when measuring PA (questionnaire vs accelerometry) and body composition (BMI, WC, skinfolds, fat mass index, dual-energy X-ray absorptiometry) and the use of different statistical approaches[46]. In addition, our population was very young (mean age 5.5 years), we used objectively measured PA and BMI for body composition. Furthermore, it is important to notice that associations between PA and body composition are not very strong and that nutrition and other factors are not discussed here[40-45]. In addition, CRF exerts greater effects on body composition and cardiometabolic risk compared to PA when studied in (older) adults[47-51] as well as in adolescents[52]. Therefore, a larger effect size of CRF is suggested compared to amount of MVPA when studying body composition and cardiometabolic risk. Indeed, CRF was cross-sectionally associated with BMI, waist circumference, HOMA insulin resistance and cardiometabolic risk in adolescents in our study (**Chapter 4**). Thus, first of all, the association between PA and BMI is not strong at young age, but this may change over the course of life. Furthermore, when studying the association between PA and health outcomes, CRF should be considered as relevant additional information.

The relationship between weight status during childhood, growth from childhood to adolescence and cardiometabolic risk in adolescence is studied in **Chapter 4**. It has become clear from other studies that both CRF and weight status are important predictors for cardiometabolic disease and all-cause mortality[53,54]. Most studies on this 'fitness-fatness' topic in children are cross-sectional and prospective evidence in children and adolescents is scarce. We found that children with higher fatness and accelerated growth in BMI from childhood to adolescence have increased cardiometabolic risk and insulin resistance during adolescence, but that a good CRF attenuates this association, especially in boys (**Chapter 4**). So, a high CRF is related to a lower cardiometabolic risk, despite unfavorable weight status. Therefore, if the aim is to improve cardiometabolic risk in adolescents, interventions need to focus not solely on reducing fatness but also on types of PA that will improve CRF.

When focussing on PA in order to improve CRF in favour of healthier cardiometabolic risk, it is relevant to know that every individual will respond differently to a certain amount of PA to manage expected health outcomes. Differences in CRF can be explained by PA engagement[55] as well as by genetic factors that influence CRF[56,57], with the heritability of time spent in MVPA estimated at 47% in adults[58]. Shared familial factors (whether genetic or environmental) play a role in the response of body composition and CRF following PA[59], which means that every individual will respond differently to a certain amount of PA. To improve CRF levels in children, the focus of guidelines for PA should switch more towards the quality of PA instead of quantity, in the way that short bursts of VPA might enhance CRF more efficiently[60-62].

Stimulating physical activity

When focussing on PA it is clear that PA is a complex multifactorial behaviour that is influenced by several factors within a socio-ecological system. For PA this socio-ecological system often includes intrapersonal factors (biological, psychological), interpersonal (social, cultural) factors, organizational factors, physical environmental (built, natural) and policies/incentives[63-66]. There is extensive literature on the impact of these factors that influence PA from birth till adolescence. This thesis mainly focused on the relation between motor skill competence, PA, CRF and health outcomes from birth till adolescence from an intrapersonal or biological approach. When approaching PA from a more interpersonal (social) perspective, parental PA in relation to children's PA is of interest. With the question mind, we studied the association between parental PA and children's PA, as parents can play a role in the PA levels of their children, (**Chapter 5**).

To study the relation between parental PA and children's PA, we used questionnaires to assess PA in parents and accelerometry to assess PA in children. Although objectively measured PA by accelerometry gives important information regarding duration and intensity of PA, it remains unknown what kind of activities are performed. Within questionnaires it is possible to ask for domain specific PA (active recreation, active transport, occupational activities and household activities). Although many studies have been published on the association between parental PA and child PA, few used objective measurements (e.g. accelerometry) to assess activity levels in preschoolers and distinguished the sex-specific relationships between parental PA and child PA as well. We found that higher levels of more intense PA in parents are associated with higher levels of more intense PA in children. These associations depended on the sex of the parent and the child (**Chapter 5**). To clarify, mothers who spent more time in vigorous PA (VPA) and more time in sports and leisure time PA had daughters who spent more time in MVPA, whereas fathers with higher levels of moderate PA (MPA) and MVPA had sons with higher levels of MVPA. Maternal PA is related to PA levels of preschoolers[67,68] and even to the PA level of infants[4,69]. Moreover, in the Melborne InFANT Program it was found that maternal PA when the child was 4 months old was positively associated with the child's PA levels at 9- and 19-months[4]. This exposure to maternal PA during infancy seems to persist into late childhood[2]. Although most studies are performed with mothers and their infants, also fathers' PA is related to the PA levels of their offspring allready at young ages (**Chapter 5**)[77]. Overall, our results emphasize the importance of parental PA during childhood and support a modelling role of parents. Therefore, to encourage PA in young children, interventions could focus on the PA of parents, taking into account that fathers are more likely to influence their sons and mothers their daughters during childhood.

Part 2. Methodological considerations and suggestions

Measurements used in our studies have their methodological strengths and limitations. In this section, we will discuss generalizability of cohort data and measures for motor skill competence and for PA used in our studies and give some suggestions for future directions.

Measuring motor skill competence

A number of motor competence screening scales, are available in the literature[70-73]. Within these tests different fine and gross motor milestones are screened. We considered motor milestone achievement as a representative for motor skill competence since motor milestones are one of the early indexes of neurological development in infancy[74]. The World Health Organization uses the gross motor milestones sitting without support, crawling on hand and knees, standing with assistance, walking with assistance, standing without assistance and walking without assistance when investigating the development of infants[15]. Five distinct gross motor milestones were assessed in two of our studies (**Chapter 3, Appendix 1**): rolling over from supine to prone position, sitting without support, hands-and-knees crawling, standing without support, and walking without support. These last four motor milestones were selected because they are used by WHO and considered universal, fundamental to the acquisition of self-sufficient locomotion, and simple to test and evaluate[75]. A high degree of inter-rater reliability confirms that these milestones are simple to administer and feasible to standardize[71,76]. In our study, caretakers were asked to assess the motor milestone achievement. The advantage of using caretakers instead of fieldworkers to report the age of achievement of motor milestones is that it is more feasible in large-scale studies. Furthermore, caretakers report an 'exact' age when they observe the achievement of a motor milestone. The fieldworkers' examinations only establishes whether or not the children meet the performance criteria for a motor milestone at the moment of assessment. The disadvantage of using caretakers is that caretakers are not trained in observing standardized criteria and it is likely that achievement of motor milestones are biased towards an earlier age. Therefore, the reliability might be lower when caregivers are asked to report the age of achievement of motor milestones.

Since the motor milestones in our studies were reported in mailed retrospective surveys the reliability of these data should be discussed. The reliability was tested in a sub cohort of our twin study by comparing mailed survey data and telephone interview data on the age at which motor milestones were achieved (sitting without support, hands and knees crawling, turning from back to belly, standing without support, and walking without support)[77]. Therefore, monthly telephone interviews with mothers of 238 twin pairs were performed, beginning at age 6 months and finishing when the infant reached the motor milestone 'walking without support'. Data from these interviews were compared with an independent group of 463 twin pairs who received the mailed survey after the second birthday. All twins were born between March 2003 and March 2004. There was no difference between the concurrent telephone interviews and the retrospective mail survey on any of the milestones, except 'standing without support', which may be because parents were not too certain if the children could really stand without support. Based on this work it can be concluded that data on achieving milestones can be reliably obtained through the mail using retrospective surveys when the children are 2 years of age. The time of mailing the survey for the GECKO cohort was at 18 months, making recall bias even less likely.

Since motor skill competence is measured differently at different ages, it is valuable to compare these measures at different ages in order to make a statement about motor milestones as a concept for motor skill competence. According to the two frequently used theoretical models for motor development[78]: 1) Metcalfe's mountain of motor development and 2) Gallahue's hourglass model, the development of motor skills is a sequential and cumulative process. Development of motor skills goes parallel with: 1) maturation of the central nervous system; 2) development of muscular strength and endurance; 3) development of posture and balance and 4) improvement of sensory processing. Therefore, a relation between infants motor milestones and children's fundamental movement skills is expected. A previous study seems to give some evidence towards a relation between gross motor milestones in infancy and motor skills measured via movement assessment battery in young children (aged 3.5 years)[79]. Hereby suggesting that achievement of motor milestones during infancy implies a comparable construct as fundamental movement skills. Furthermore, the later achievement of motor milestones we found in our study (**Chapter 3, attachment A**) is comparable with the lower scores over time found in older children[9,10]. Although, the results are measured in different populations, it gives support for the idea that motor milestone achievement and fundamental movement skills measure the same construct.

Since the motor milestones rolling over, crawling and walking without support also implies movement, it should be discussed whether these motor milestones are motor skills rather than PA. Motor skills are necessary to make movements and therefore they are the forerunner of PA. PA is evaluated more as a quantitative measure, as in the amount of time the body is moving, while motor skills are evaluated as a qualitative measure, as in being able to perform a certain skill. However, the question remains whether motor milestones and PA might have a same underlying construct which influence motor skill competence as well as PA. This construct might be genetic or an internal driven factor like personality and an intrinsic urge to be active. In conclusion, when measuring motor skill competence during infancy, the use of infant motor milestone achievement seems useful as a construct of motor skill competence since it is related to later fundamental movements.

Measuring physical activity

Assessing PA is challenging since PA is multidimensional and complex behaviour to measure. There is no single method that can capture all subcomponents and domains in the activity of interest. The use of accelerometers to assess SB and PA has advantages over self-report measures such as the ability to track intensity, duration, and frequency of free-living PA, without relying on participants to recall their PA[80,81]. Accelerometers have been proven feasible, reliable and valid for assessing PA in children[82-84]. Among the commercially available brands, the ActiGraph (Pensacola, FL, USA) accelerometers are the most frequently used by researchers[85]. The first Actigraphs used in studies were uniaxial (vertical axes was detected) and accelerations could be converted into estimates of energy expenditure, stepcounts, and time spent in SB, light PA (LPA), MPA, VPA, moderate and vigorous (MVPA) and total (TPA). The Actigraph GT3X+ accelerometer, released in 2009, is three-axial, meaning that accelerations are captured in three directions, which may be better to capture the movement of young children, since they move in a different way than adults. The continuous development in data capture and data processing of these devices makes it difficult to compare data between studies. Due to the rapid development in this technology, there is an overwhelming amount of data collection and processing criteria decisions. In addition, there is no consensus about which approaches to use. Therefore, we will discuss two relevant issues regarding the use of the three-axial Actigraph. Two important issues are relevant: 1) Use of epoch (time unit in seconds in where acceleration is averaged); 2) Use of cut points to estimate outcomes (time spent in SB, LPA, MPA, VPA, MVPA and TPA).

Epoch

When assessing children's PA via accelerometry, the selection of an epoch length is important. Epoch length refers to the interval of time over which the units of accelerometer measures are summed. The epoch length influences results of estimated PA outcomes[86-89]. In our GECKO Drenthe cohort we compared minutes in different PA levels for different epoch lengths of 5, 10, 15, 30 and 60 seconds. We found differences up to 60% for VPA, with means and SD of 102 ± 42 minutes VPA when using 5 second epochs versus 33 ± 21 minutes when using 60 seconds epoch. These large differences are most specific for higher intensity PA. Although the absolute estimation for the amount of time spent in SB, LPA, MPA or VPA can vary because of epoch length, the variation in ranking between children relative to each other remains fairly the same. The use of smaller epochs up to 1 seconds might overestimate PA[87]. On the other hand, larger epochs of 60 seconds might not catch the sporadic movements of children[86,88]. Epochs between 5 and 15 seconds seem to be useful for children to measure intermittent and sporadic patterns of children's PA but without overestimating PA.

Cut points

Although numerous studies designed to calibrate and validate accelerometers have been conducted, there is no standardized methodology to translate accelerometer output into an estimate of PA[90,91]. Cut points are developed based on counts using acceleration of one (vertical) or three axes and based on the site for placement (hip, thigh, wrist or ankle). For children, specific cut points are developed based on one axis[92,93] or three axes[94] for when the Actigraph is placed on the hip. Other cut points are developed when the Actigraph is worn on the wrist[95,96]. With multiple cut points available, comparing results from different studies is difficult. Differences in estimates in minutes of MVPA ranges from 38-80% across children aged 6-10 years of age when using different cut points[88,93,97]. These differences in estimates make clear that the validity of time spent in SB, LPA, MPA, VPA, MVPA and TPA is not satisfactory. The lack of consensus in collecting and processing Actigraph data makes it difficult to compare estimates of children meeting PA guidelines. The choice of hip placement in our studies was a logical one since, at the time of study performance, the use of hip placement was traditional and well validated. In addition, no cut points for wrist-worn Actigraphs were available. The decision to use Butte's cut points[94] was logical since it was based on three axes, hip placement and the right age group. During recent years the use of wrist placement is been increasing used as it has been shown to yield superior compliance in children, compared with hip placement[98]. Although 2 studies have developed cut points for the use of wrist-worn three axial accelerometers, development of age-specific cut points should be encouraged.

Future perspectives for measuring physical activity

It remains a challenge to estimated the right intensity and thereby the estimated energy expended for PA when using accelerometry. Development of the current hardware technology allows the capture and storage or transmission of large volumes of raw acceleration signal data when measuring PA. This gives opportunities to improve characterization of PA. However, the opportunities are accompanied by logistical and analytical challenges. Tackling these analytical challenges together with advances in data storage, transmission, and big data computing will minimize logistical challenges. Last decade, the focus was on developing algorithms for PA energy expenditure based on activity counts to catagorize data into SB, LPA, MVP and VPA based on metabolic equivalent. However, the developed algorythms do not always estimate the activity well. Cycling, for instance, is an activity which is often underestimated when using accelerometry[99]. Nowadays the attention has more shifted towards activity characterization and energy expenditure estimation based on features extracted from raw acceleration signals[100]. To explain, if a movement pattern is recognized as playing tennis or cycling based in specific features in accelerations, it is possible to estimate more exact how much energy is expended. Recognizing the features of these activities gives more information about the kind of activity performed. Although it is preferable to find consensus for an analytic method when measuring PA with accelerometry, optimizing and developing the measurement of PA (for example by characterizing PA per activity) could give much more information and insights.

In addition to the development of characterizing specific PA patterns there is a growing interest in epidemiological research for reallocation of different PA behaviours. Most studies in the past have analysed the associations of sleep, SB, LPA, MPA, VPA and MVPA in isolation from each other; that is, without taking into account the displacement of time spent in the remaining behaviours. The current evidence indicates that time reallocation between sleep, SB, LPA, and MVPA may be of special interest when studying the associations with a number of health outcomes[101] . Indeed, in youth replacing time spent SB with MVPA was associated with total body fat percentage, but not with BMI or waist circumference[102]. This methodology for analysing PA in relation to health outcomes is under development and will advance the field.

Generalizability

With regard to the use of data of twins, the generalizability towards singletons can be argued. Within the normal window of achievement of motor milestones of 'het van Wiechenschema'[103], there are no major differences in reaching the different motor milestones (**Appendix 1**). Although within the normal window of development there are no major differences, singletons reach their exact moment of milestones a little earlier compared to twins, since twins are born with a shorter GA and therefore have less time to develop in utero. When comparing the motor milestone 'walking without support' from the singletons (**Chapter 2**) of our GECKO Drenthe cohort with twin data from the Dutch Twin Registry (**Chapter 3**) we see that singletons walk without assistance at the age 14.1 ± 1.9 and twins at the age of 14.8 ± 2.3 months. However, the mean GA in the singletons from GECKO Drenthe cohort is 39.9 ± 1.6 weeks and in the twins from the Dutch Twin Registry it is 37.0 ± 2.0 weeks. We observed a linear association between GA and age of achieving motor millstones, with twins who are born with 40 weeks of GA walk without assistance with 14.2 ± 2.3 months. This is very comparable to singletons born with 40 weeks of GA. When studying the relation between motor milestones and BMI in our twin population, we adjusted for GA. Babies born pre-term (before 32 weeks of GA) or with very low BW (<1500 grams) are considered at risk for motor development deficits[104] and are therefore not included in our studies. Regarding the generalizability of the outcomes of our twin study focusing on the association between motor milestones and BMI it can be mentioned that, although there is a difference in growth between twins and singletons during the first 2.5 years of life, twins catch up in their body size[105]. Since we used BMI after age 2, we expect that the association between motor milestones and subsequent BMI age 2, 4, 7 and 10 years of age we found in twins will be comparable to that in singletons.

In conclusion, the use of accelerometry in children to measure PA seems feasible, reliable and valid. When using Actigraphs in children, 5, 10 or 15 second epochs should be used to capture intermittent and sporadic PA. The choice of cut points is depending on the site of wearing, the use of uni- or three-axial accelerometry and the age group. In addition, it should be mentioned that, beside the discussion of accelerometer placement on the body, epoch time and cut point at different ages, there is no measure that can assess all facets of PA since PA is a multi-dimensional construct. For example, questionnaires can still be useful when studying domain specific PA behaviour and heart rate monitoring could add more specific individual information when evaluating health effects. Researchers should consider advantages and limitations of different measures depending on the specific outcomes of interest. For many studies, combining multiple PA assessments is recommended. Technological developments as well as new statistical approaches can give more insight in the relation between different PA behaviours and health outcomes.

Part 3. Directions for future research

Intervention studies

Since we found an association between infant motor milestone achievement and subsequent PA (**Chapter 2**), it is interesting to find out whether infant motor milestone achievement could be stimulated via interventions. In the Netherlands, assistants in Well Baby Clinics stimulate the parents to put their baby in prone position whenever possible and provide them with instructions and tips how to do this. Whether giving these instructions is an effective strategy to promote prone position is unknown, but activity stimulation during the first year of life was found to improve indicators of subsequent adiposity[106]. When growing older, infants should be encouraged to spent as much time as possible moving unrestricted, since this may contribute to a healthy growth pattern[35]. Beside the role of parents/caregivers for stimulating prone position and spending time playing unrestricted during infancy, parents/caregivers can play a role in stimulating PA during childhood. PA levels of the child are related to PA levels of parents/caregivers

(**Chapter 5**). Enhancing PA both in school and in the home environment should be taken into consideration to stimulate PA in children. Especially for less active children, the weekends might be a possible time to enhance their PA[107] and parental support is suggested to stimulate PA in children[108]. Future research should focus on the use of the intervention mapping protocol for implementing an effective intervention to stimulate the development of motor skill competence during infancy and PA during childhood[109], keeping track of motor skill competence, PA and health outcomes as well as behavioral aspects in parents.

Long-term consequences and physiological pathways

There is a lack of physiological insights into the underlying mechanisms and direction of pathways of the associations between motor skill competence, PA, CRF and health outcomes from birth to adolescence. We hypothesized that PA could mediate the relation between early motor skill competence and weight status and health (**Chapter 2**), but we found no supportive evidence. However, we found an association between early motor skill competence and subsequent PA (**Chapter 2**). Although there is some evidence for a reciprocal relation between motor skill competence and PA from childhood to adolescence[7], future research could focus on younger populations to find out if these reciprocal associations already exist from birth onwards. Furthermore, we found that CRF attenuates metabolic risk in adolescents (**Chapter 4**). So, we should not only look at PA levels at different ages in children, but also at CRF in different ages of children, as in adults, since CRF seems a stronger predictor for cardiometabolic risk compared to PA or SB[53,54,110]. More specifically, we suggest that lower cardiometabolic risk due to higher CRF could be established by higher intense PA[60-62]. Therefore, infants should be tracked on weight status, motor skill competence, PA, CRF and health outcomes from birth to adolescence to address physiological insight and reciprocal pathways.

Part 4. In summary

It seems relevant to consider motor skill competence stimulation in infants when focusing on childhood PA. Infants who achieve their motor milestones later are physically less active and more sedentary when growing older. However, the effects are small. Motor milestones can be seen as benchmarks of development in where motor coordination is central and may lead to more movement opportunities to increase PA. Although we found that infants reach their motor milestone later over the past decades, motor milestone achievement and BMI during childhood are largely independent. Also PA was not associated with BMI during young childhood. Instead of PA, CRF might have a stronger association with health outcomes during adolescence. Higher BMI was associated with subsequent cardiometabolic risk and an increase in BMI between childhood and adolescence was associated with cardiometabolic risk when taken baseline BMI into account. A good CRF reduced this association. Therefore, stimulating MVPA and especially VPA to increase CRF is advised during childhood. PA during childhood could be stimulated by focussing on early motor milestone achievement and by involving parents as a role-model for PA. For future studies, and comparability of studies, it would be good to have guidelines for the use and data processing of accelerometry data. Furthermore, we advise to combine accelerometry data with other measurements, like questionnaires to define the nature of the activities, and to measure CRF, because it may be more relevant for health outcomes than PA alone.

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CHAPTER 7

SUMMARY

NEDERLANDSE SAMENVATTING

DANKWOORD

LIST OF PUBLICATIONS AND PRESENTATIONS

SHARE DISSERTATIONS

SUMMARY

The rising prevalence of childhood overweight and obesity are of clinical interest because obesity tracks into adulthood and associates with health problems like metabolic risk factors for cardiovascular disease. Since low levels of physical activity (PA) are a contributing factor to overweight, obesity and cardiometabolic risk, and since PA tracks during the life course, higher levels of PA during childhood may also have benefits later in life. Therefore, it lays good foundations for an active life and healthy ageing. Focusing on early life determinants of motor skill competence and PA might therefore be useful when developing strategies to prevent overweight and obesity at young age.

The general aim of this thesis was to study how motor skill competence, PA, cardiorespiratory fitness (CRF), weight status and cardiometabolic risk relate to each other during development from infancy to adolescence. To get insight in contextual factors, the relationships between motor skill competence, PA and weight status was studied from a temporal perspective comparing different cohort over time as well as from a social perspective studying parental influence by looking at parental behavior. For this, three healthy populations within the Netherlands between the ages of 0-16 years were used: Young Netherlands Twin Registry (YNTR), Groningen Expert Center for Kids with Obesity (GECKO) Drenthe cohort and Tracking Adolescents' Individual Lives Survey (TRAILS).

In **Chapter 2** we found evidence for an association between the age of reaching infant motor milestones to subsequent PA levels in the GECKO Drenthe cohort. Infants who achieved walking without support at an older age, but within the normal range of development, spent more time in sedentary behavior and less time in moderate-to-vigorous PA when aged 5 years. The differences in levels of childhood sedentary behavior and PA associated with infant motor milestone achievement were subtle. Although, infants who achieve walking without support at an older age have lower levels of PA, the age of achieving walking without support was not related to subsequent BMI at different ages.

Taking into account the population-wide increase in childhood overweight, we studied the relation between motor milestone achievement and BMI also from a temporal perspective in **Chapter 3** using YNTR data. Infants born in the later cohorts achieved their motor milestones at an older age compared to those born in earlier cohorts. These differences were most pronounced for the motor milestones ‘standing without support’ and ‘walking without support. Infants born in 2007 were able to stand and walk without support approximately 1 months later compared to those born in 1987. The increase in the prevalence of overweight at age 10 however, was independent of the population shift in

age of achieving motor milestones. This is in line with the findings of **Chapter 2**, that motor milestone achievement and BMI during childhood were not related. Thus, using **Chapter 2** and **3**, a direct pathway from motor skill competence to lower rates of overweight, could not be confirmed.

When studying the association between PA and health outcomes, CRF should be considered as relevant additional information. In **Chapter 4** we found that children from the GECKO Drenthe cohort with higher fatness and accelerated growth in BMI from childhood to adolescence have increased cardiometabolic risk and insulin resistance during adolescence, but that a good CRF attenuates this association, especially in boys. So, a high CRF is related to a lower cardiometabolic risk, despite unfavorable weight status. Children with a more healthy weight and a higher aerobic fitness have the lowest cardiometabolic risk.

When focussing on PA it is clear that PA is a complex multifactorial behavior that is influenced by several factors within a socio-ecological system. Therefore, we focused in **Chapter 5** on the association between parental PA and children's PA, as parents can play a role in the PA levels of their children. Using the TRAILS data, we found that higher levels of more intense PA in parents are associated with higher levels of more intense PA in children. These associations depended on the sex of the parent and the child. To clarify, mothers who spent more time in vigorous PA and more time in sports and leisure time PA had daughters who spent more time in moderate-to-vigorous PA, whereas fathers with higher levels of moderate PA and moderate-to-vigorous PA had sons with higher levels of moderate-to-vigorous PA.

Chapter 6 provides a general discussion of the studies described in this thesis. Overall, this thesis shows that later achievement of motor milestones during infancy is linked to lower levels of PA during childhood. At the same time, this later achievement of motor milestones does not seem to be related to weight status during childhood. In adolescents, those with higher adiposity during childhood and with accelerated gain in body mass index (BMI) from childhood to adolescence can compensate for cardiometabolic risk with higher CRF. To stimulate PA, parents can act as role models since parental PA is related to childhood PA in a sex-linked manner. Stimulating CRF enhancing PA seems most relevant when improving cardiometabolic health.

NEDERLANDSE SAMENVATTING

INLEIDING

Het percentage kinderen dat overgewicht of obesitas heeft wereldwijd, is in de afgelopen decennia enorm gestegen. Ook in Nederland speelt dit gezondheidsprobleem. In 2018 had 11.7% van de kinderen tussen 4 en 17 jaar overgewicht, waarvan 9% matig overgewicht en 2.7% ernstig overgewicht (obesitas). Het hebben van overgewicht of obesitas op jonge leeftijd is een groot probleem omdat het een grotere kans geeft om later ook overgewicht of obesitas te houden. Hierdoor hebben deze kinderen ook een grotere kans op cardiometabole gezondheidsrisico's zoals hoge bloeddruk, diabetes type II en hart- en vaatziekten te ontwikkelen.

Minder bewegen kan, net als ongezondere voeding, bijdragen aan het ontwikkelen van gezondheidsrisico's. Kinderen die minder bewegen, bewegen op oudere leeftijd gemiddeld ook minder waardoor ze later in hun leven ook meer gezondheidsrisico's kunnen ervaren. Wanneer we het probleem van overgewicht en de gezondheidsrisico's die hiermee gepaard gaan aan willen pakken, dan zouden we het beste al op jonge leeftijd moeten beginnen met het stimuleren van bewegen.

Een van de factoren die relevant zou kunnen zijn waardoor het bewegen van kinderen op jonge leeftijd gestimuleerd kan worden, is de vroeg motorische ontwikkeling. Kinderen die zich motorisch sneller of beter ontwikkelen, hebben immers meer mogelijkheden om te bewegen. En omdat meer bewegen gerelateerd is aan gezondheidsvoordelen, zou een snellere of betere motorische ontwikkeling gezondheidsvoordelen kunnen geven zoals een gezonder gewicht. Het kan ook andersom zijn dat kinderen die juist wat zwaarder zijn, minder gaan bewegen en zich daardoor motorisch ook minder snel of goed ontwikkelen. Als kinderen minder bewegen, zijn ze vaak ook minder fit. Deze slechtere aerobe fitheid kan zorgen voor meer gezondheidsrisico's.

Het doel van de studies in dit proefschrift was om bij kinderen van 0-16 jaar meer te weten te komen over de relaties tussen vroege motorische ontwikkeling, bewegen, aerobe fitheid, overgewicht en cardiometabole gezondheidsrisico's. We hebben ook naar veranderingen in overgewicht door de jaren heen gekeken en bekeken of motorische ontwikkeling van invloed is op deze veranderingen in overgewicht. Tot slot groeien jonge kinderen voor een groot deel op bij hun ouders/verzorgers en hebben we ook gekeken naar de relatie tussen het beweeggedrag van kinderen en hun ouders.

RESULTATEN EN CONCLUSIES

In **hoofdstuk 2** van dit proefschrift hebben we aangetoond dat kinderen die later de motorische mijlpaal 'los lopen' bereiken minder bewegen en meer zitten of liggen wanneer ze 5 jaar oud zijn. Kinderen die met 14 maanden kunnen lopen, bewegen gemiddeld 28 minuten per week (4 minuten per dag) minder en zitten/liggen gemiddeld 49 minuten per dag (7 minuten per dag) meer dan kinderen die met 12 maanden kunnen lopen. Dit verschil is niet heel erg groot, maar draagt wel significant bij aan het meer bewegen. Hoewel de kinderen die zich motorisch sneller ontwikkelen op kinderleeftijd meer bewegen, hebben zij niet een lagere BMI in vergelijking tot kinderen die zich trager ontwikkelen. Er lijkt dus geen verband te bestaan tussen motorische ontwikkeling in de eerste 18 levensmaanden en overgewicht op 5-jarige leeftijd.

In **hoofdstuk 3** hebben we nogmaals gekeken naar de relatie tussen de motorische ontwikkeling en overgewicht, maar dan vanuit het perspectief van tijd (tweelingen geboren tussen 1987 en 2007). We hebben gevonden dat kinderen die in 1987, of in de jaren vlak daarna, zijn geboren, eerder hun motorische mijlpalen bereikten dan kinderen die in latere jaren zijn geboren. Dit verband was lineair en het meest zichtbaar in de motorische mijlpalen 'los staan' en 'los lopen'. Kinderen die in 1987 zijn geboren konden gemiddeld een maand eerder los staan of lopen in vergelijking tot kinderen die geboren zijn in 2007. Verder zagen we dat het percentage kinderen met overgewicht alleen op 10-jarige leeftijd minimaal was gestegen en niet op jongere leeftijden. De vertraging in het behalen van de motorische mijlpalen in de afgelopen twee decennia verklaarde echter niet de (minimale) stijging in het percentage kinderen met overgewicht op 10-jarige leeftijd. Dit komt overeen met de bevinding uit **hoofdstuk 2**, waarin we ook geen relatie tussen motorische ontwikkeling en BMI/overgewicht hebben gevonden.

Wanneer de relatie tussen bewegen en gezondheidsuitkomsten wordt bekeken, dan zou er rekening gehouden moeten worden met aerobe fitheid. Uit andere studies weten we dat meer bewegen leidt tot een betere aerobe fitheid, maar ook dat bewegen en aerobe fitheid los van elkaar van invloed zijn op gezondheidsvoordelen. Uit onze studie in **hoofdstuk 4** bleek dat kinderen met een hogere aerobe fitheid minder gezondheidsrisico's hebben. Verder bleek dat kinderen die rond hun 11^de^ een hogere BMI hebben, grotere gezondheidsrisico's hebben in vergelijking tot kinderen die een lagere BMI hebben. De mate waarin de BMI tussen het 11^de^ en 16^de^ stijgt, geeft, onafhankelijk van de BMI op 11 jaar, ook nog een extra verhoogd gezondheidsrisico. Dit gezondheidsrisico van een hogere BMI en meer groei in BMI tussen je 11^de^ en 16^de^, wordt veel minder groot wanneer kinderen met een hogere BMI ook een hogere aerobe fitheid hebben. Vooral bij jongens geldt dit. Dus ondanks een hogere BMI, zorgt een goede aerobe fitheid voor minder gezondheidsrisico's. Kinderen die een gezonde BMI en een goede aerobe fitheid hebben, hebben de laagste gezondheidsrisico's.

Bewegen is een heel complex gedrag dat door heel veel verschillende factoren in een sociaalecologisch systeem wordt beïnvloed. Daarom hebben we ons in **hoofdstuk 5** gefocust op de omgeving van het kind. We hebben gevonden dat wanneer ouders meer intensief bewegen, hun kinderen dat ook doen. Deze relatie tussen het bewegen van ouders en kinderen is afhankelijk van het geslacht van de ouder en het kind. Om dit te verduidelijken: moeders die meer tijd aan intensief bewegen spendeerden hadden ook dochters die meer tijd doorbrachten met intensief bewegen. Vaders die meer tijd aan intensief bewegen spendeerden hadden ook actievere zonen.

In **hoofdstuk 6** worden alle studies uit dit proefschrift bediscussieerd. Samenvattend laat dit proefschrift zien dat het later behalen van motorische mijlpalen in de eerste anderhalf jaar na de geboorte, gerelateerd is aan minder bewegen en meer zitten/liggen op 5-jarige leeftijd. Maar het later behalen van motorische mijlpalen lijkt geen relatie te hebben met de BMI in de kindertijd. Kinderen met een hogere BMI en een sterkere BMI toename van kindertijd naar adolescentie, hebben een groter gezondheidsrisico in vergelijking tot kinderen met een lager BMI en minder grote groei. Maar een goede aerobe fitheid zorgt dat het gezondheidsrisico bij kinderen met een hogere BMI en een sterkere BMI toename, minder groot wordt. Om bewegen te stimuleren zouden ouders als rolmodel kunnen fungeren omdat het bewegen van kinderen gerelateerd is aan het bewegen van hun ouders. Het stimuleren van intensief bewegen, waardoor een hogere aerobe fitheid wordt bereikt, is van belang om de gezondheid van kinderen en adolescenten te beïnvloeden.

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Silvia, april 2020

"Meningen zijn als spijkers: hoe vaker je erop slaat, hoe dieper ze doordringen."

LIST OF PUBLICATIONS AND PRESENTATIONS

Peer-reviewed publications

Brouwer SI, Stolk RP, Bartels M, van Beijsterveld CEM, Boomsma DI, Corpeleijn E. Infant motor milestones and childhood overweight: over two decades trends in a large twin cohort. Int J Environ Res Public Health. 2020;*17(7):2366*

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Presentations

Nov 2016	Oral presentation Dag van het Sportonderzoek, Groningen, the Netherlands
Oct 2014	Oral presentation International Congress on Physical Activity and Public Health, Rio de Janeiro, Brazil
Oct 2012	Oral presentation International Congress on Physical Activity and Public Health, Sydney, Australia
Mei 2011	Oral presentation European Diabetes Epidemiology Group, Jerez de la Fonteira, Spain
Nov 2011	Oral presentation Dag van het Sportonderzoek, Amsterdam, the Netherlands
Jun 2010	Oral presentation Scientific Meeting Tracking Individual Life Survey, Groningen, the Netherlands
Dec 2009	Oral presentation at Congres van Vereniging voor Sportgeneeskunde, Noordwijkerhout, the Netherlands
Okt 2009	Oral presentation at the Highlights of the European Association for the Study of Diabetes, Utrecht, the Netherlands (nomination Pfizer award)
Sept 2009	Poster presentation at 45th Annual Meeting of the European Association for the Study of Diabetes, Vienna, Austria

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APPENDIX

INFLUENCES ON ACHIEVING MOTOR MILESTONES: A TWIN SINGLETON STUDY

Silvia I. Brouwer, Toos C.E.M. van Beijsterveld, Meike Bartels, James J. Hudziak, Dorret I, Boomsma

Twin Res Hum Genet. 2006; 9(3):424-30

ABSTRACT

Background

In order to determine if twinning impacted achievement of motor milestones the attainment of early motor milestones in twins was examined and compared to published data from singletons of the same age from the same culture and birth years. We examined the influence of twinning, sex, zygosity and birth cohort (1987–2001) on the motor development of twins aged 0 to 24 months.

Methods

Data on the attainment of motor milestones (turn, sit, crawl, stand and walk) of twins were collected from maternal reports. All data were corrected for gestational age. Data from the twin sample were compared to normative data from singletons, which were available from Child Health Clinics (CHC).

Results

Analyses across twin data and the CHC singleton data revealed no differences between twins and singletons in achievement of motor milestones. Girls were able to sit without support slightly earlier than boys, otherwise there were no other sex differences. Birth-order analyses revealed minimal but significant differences in turning over from back to belly and for sitting without support between the first- and second-born. Dizygotic (DZ) twins were faster than monozygotic (MZ) twins in achieving the moment of sit, crawl, stand and walk. Twins born in earlier cohorts were faster in reaching the moment of crawl, sit and walk.

Conclusion

It is concluded that there are no differences in time of reaching motor milestones between twins and singletons within the normal range. Sex has minimal to no effect on motor development in early childhood. DZ twins achieve motor milestones sooner than MZ twins. Attainment of gross motor milestones (crawl, stand and walk) is delayed in later birth cohorts.

INTRODUCTION

Twin studies have been fundamental to the investigation of genetic contributions to multiple phenotypes, whether they be quantitative (e.g. IQ, height) or categorical (e.g. attention-deficit/hyperactivity disorder). In the field of behavioural genetics, twin populations have been used to study the genetic and environmental contributions to a variety of, for example, cognitive, personality and psychiatric traits or illnesses. The data that result from these studies are used to drive family and sib-pair analyses and hunt for specific genetic and environmental factors. There is, however, debate about the utility of the twin model in the study of human behaviour. Are the results generalizeable to nontwin populations? With recent reports of gene–environment interactions, and epigenetic phenomena in the etiology of psychopathology, it is reasonable to ask just how closely data from twin studies relate to singleton data. One proxy for testing the environmental effects of twin births is to relate early developmental milestones between twins and singletons to determine twin behaviour deviates from that of singletons. One such method would be to test the achievement of major developmental milestones of twins and singletons and determine the relative variance across these groups and then within twins, by birth order, sex, and zygosity status.

The rationale for this work is relatively straightforward. Twins weigh less than singletons even when born full term (born between 36 and 41 weeks of gestation)[1-3]. Twins are born preterm more often than singletons. Several studies report that a delay in motor development is associated with low birthweight and shorter gestational age (GA)[4-10]. Therefore, when studying the early motor development in twins, GA should be taken into account[11].

The attainment of gross motor milestones is an important indicator of child development. Such milestones include turning over from back to belly (turn), crawling on hands and knees (crawl) and sitting (sit), standing (stand) and walking (walk) without support[12-14]. Attainment of these milestones may be of clinical importance for detecting delays. Delays in motor milestone achievement are thought to be an indicator of abnormal development. It is therefore important to identify the factors that influence the normal range of attainment for motor milestones. In Child Health Clinics (CHC) in the Netherlands, reference values of motor milestones of 'het van Wiechenschema' are used (turn = 6 months; sit = 9 months; crawl = 12 months; stand = 15 months; walk = 18 months) to screen infants for possible delays. These values were derived from a study carried out in the early 1970s by Schlesinger-Was (1981)[15]. Schlesinger-Was reported the age upon which 90% of the infants reached a certain milestone. To establish whether these reference values were still useful in the 1990s, Verkerk and colleagues (1993)[16] used data on motor milestones from the 'Social Medical Survey of Children Attending Child Health Clinics' (SMOCC) study[17] to investigate reference values used by Schlesinger-Was. The SMOCC is a population-based, observational, follow-up study of a cohort of Dutch children investigated from birth to 24 months of age. Good agreement was found between the reference values in the SMOCC study and the values reported at the CHC. As these data are primarily from singletons it is important to determine if these same reference values are useful for twins. This investigation is the first goal of this report. We will determine if reference values developed primarily in the study of singleton births are applicable to twin births.

Several studies have shown sex differences in motor development during childhood and adolescence as reviewed by Thomas and French[18]. But when these changes in motor development emerge is still uncertain. Within our sample of infant twins aged between 0 and 24 months we will examine if sex differences exist during the first 2 years of life. As monozygotic (MZ) twins are seen as more vulnerable than dizygotic (DZ) twins due to an excess of structural defects[19-21] an effect of zygosity on motor development is also examined in this report.

Data of gross motor milestones have been collected in the last 15 years (1986–2001) by the Netherlands Twin Register (NTR). We divided all twins into different birth cohorts to examine possible cohort effects. Due to a change in clinical practice which changed the advice for sleep position in the early 1990s, a change might be expected in the time of attaining motor milestones since parents are advised to put their children to sleep in the supine (on the back) position rather than the prone (on the belly) position. Several studies have stated the effect of sleep position on motor development[22-27]. Prone sleepers/players attain several motor milestones earlier than supine sleepers/players.

To summarize, we examined the early motor development of healthy twin pairs from the NTR born between 1987 and 2001. To see whether motor development of twins is comparable to that of singletons in the Netherlands, we compared our data of motor milestones from twins with the SMOCC study. We looked at the effects of sex, birth order, zygosity and birth cohort on measures of motor development of twins corrected for GA.

METHODS

This study is part of a longitudinal study on early child development. Data on 11,712 pairs of twins born between 1986 and 2001 were obtained from surveys collected by the NTR, with questions about zygosity, birthweight, GA and motor milestones. Forty to fifty per cent of all multiple births in the Netherlands are registered by the NTR[28,29]. Participation in research is voluntarily. For this study on motor development two hundred 48 pairs were excluded because either one or both of the children had a disease or serious mental or physical disability which could influence the development. Since this article concerns motor development, we also left out 73 twin pairs with milder physical disabilities like clubfoot, hip deviation and hypo- or hypertension in muscles. A relative healthy group of 11,391 pairs of twins remained for analysis. From these twin pairs 3773 (33.1%) were MZ and 7618 (66.9%) were DZ. Information about the zygosity of twins was obtained from questions in questionnaires collected at the age of 3 and/or 5, 7, 10, 12 years[30] and from Blood/DNA typing (n=1059). There were 11,357 (49.9%) boys and 11,417 (50.1%) girls. The 11,391 pairs of twins born between 1987 and 2001 were subdivided into five cohorts (1987–1989 = cohort 1, 1990–1992 = cohort 2, 1993–1995 = cohort 3, 1996–1998 = cohort 4 and 1999–2001 = cohort 5).

To test if motor development of twins is comparable to the motor development of singletons we selected a group of twins from this study comparable to the cohort of children used in the SMOCC study. The SMOCC study is a population-based, observational, follow-up study of a cohort of children born 1988 to 1989. The SMOCC birth cohort consisted of 2151 live-born infants (49.2% boys, 50.8% girls). To establish reference values for healthy children some groups were excluded: children from non-West European countries; children with a developmental disorder detected at CHC and confirmed by specialists; children with a disorder which can influence their development from average (like clubfoot or spasm) and children with birthweight less than 2500 grams or GA less than 37 weeks. Children in the SMOCC study were examined by the physician and the district nurse at the ages of 1, 2, 3, 6, 9, 12, 15, 18 and 24 months in CHC. The physician or district nurse reported if a motor milestone was obtained during these examinations. A twin sample matched on year of birth (1988–1991), birthweight (>2500 grams) and GA (>36.5 weeks) was selected from the NTR.

Measures

Information from the twins on birthweight and GA was obtained by maternal rating from a first questionnaire which was sent shortly after the twins were born. Birthweight was measured by a doctor or nurse shortly after birth. Parents were asked to report these birthweights. With this questionnaire parents received a list to keep track of important motor milestones (turn, sit, crawl, stand, walk). In a second questionnaire, mailed out when the twins were at the age of 2, parents were asked to report the age in which the motor milestones were reached. Those motor milestones were turning over from back to belly (turn), sitting without support (sit), crawling on hands and knees (crawl), standing without support (stand) and walking without support (walk). Twin data on motor milestones were compared with data on motor milestones of singletons according to reference values of 'het van Wiechenschema'. Missing values for each motor milestone were between 2.3% and 9.7%.

Statistical Analyses

Differences between first- and second-born were tested by paired *t* tests. As data from twins are not independent, we only present analyses based on data of the first-born twin (we only noted a small difference for obtaining the moment of turn and sit) on motor milestones. The Statistical Package for Social Science 11.5 (SPSS) was used to analyse the data. Frequency analyses were used to compare the percentage of twins and singletons that attained TURN within 9 months, SIT within 12 months, CRAWL within 15 months and WALK within 18 months. Cross-tabulations were used for analysis of the percentages MZ and DZ twins in different cohorts.

For every motor milestone, means of the motor milestone from MZ and DZ twins were compared over different cohorts. ANOVA was carried out with sex (male/female), zygosity (MZ/DZ) and cohort (1–5) as between factors and GA as a covariate. Because of the high correlation between GA and birthweight we only used GA as a covariance.

Table 1 Percentage twins and singletons who reached motor milestones by a fixed age

Motor milestone	MZ twins NTR (n)	Percentage MZ twins	DZ twins NTR (n)	Percentage MZ twins	Singletons SMOCC (n)	Percentage singletons
Turn 9 months	719/747	96%	1499/1554	97%	970/1039	93%
Sit 12 months	761/770	99%	1578/1594	99%	1046/1059	99%
Crawl 15 months	735/749	98%	1556/1581	98%	871/912	96%
Walk 18 months	752/786	96%	1576/1645	96%	822/860	96%

To test whether girls from same-sex pairs (FF) differed from girls of opposite-sex pairs (FM/MF), and likewise if boys from same-sex pairs (MM) differed from boys of opposite-sex pairs, ANOVA was carried out both for the group of girls and the group of boys with same-sex or opposite-sex pair as a factor.

RESULTS

Twins Versus Singletons

Table 1 shows the percentage of singletons and a selected group of MZ and DZ twins who reached a certain motor milestone (turn, sit, crawl and walk) at a fixed moment (9, 12, 15 and 18 months, respectively) as used by 'het van Wiechenschema'. For turn, sit, crawl and walk a minimum frequency of 90% of the twins had reached the motor milestones at the age of 9, 12, 15 and 18 months, respectively. Comparison between MZ and DZ twins and singletons who reached a certain motor milestone at a fixed moment showed a few small differences. For turn and crawl the proportion MZ and DZ twins who reached these milestones at a fixed moment were slightly higher than singletons.

There was a significant decrease in GA over the cohorts (p<0.001). This linear effect went from 37.1 weeks in cohort 1 to 36.5 weeks in cohort 5. Conforming to other studies (GA; Allen & Alexander, 1990; Cheung *et al*., 2001; Den Ouden *et al*., 1991; Goyen & Lui, 2002; Lems *et al*., 1993; Lui *et al*., 2001; Piper *et al*., 1989) we found that the effect of GA was significant for all motor milestones (p<0.001). Pearson correlations were –0.246 for turn, –0.249 for sit, –0.191 for crawl, –0.236 for stand and –0.246 for walk. Therefore we used GA as a covariate in all analyses and results. There was a highly significant correlation between birthweight and GA of 0.736 (p<0.001). Because of this high correlation we only used GA as a covariate.

Sex and Birth Order

Girls were faster than boys (p<0.001) for sit only. There were no differences between DZ girls from same-sex or opposite-sex twin pairs (DOS). For DZ boys from same-sex or DOS pairs no differences were found either. There were some small, but significant differences between first- and second-born twins. First-born twins were faster than second-born twins for turn (p=0.001) and sit (p=0.003). These differences in means were only less than 0.043 months (<1.5 days). For crawl, stand and walk no differences were found. Therefore, we report for all other analyses on data of the first-born twin.

Zygosity

There was a significant increase in the percentage of DZ twin pairs over the cohorts (p<0.001) ranging from 62.8% in cohort 1 to 70.3% in cohort 5. Differences for mean GA between MZ and DZ twin pairs were significant (p<0.001). MZ twin pairs are born at 36 weeks and 3 days, DZ twin pairs are born at 36 weeks and 6 days. The percentage of twins who were born before 32 weeks was 3.8% for DZ twins and 4.5% for MZ twins. DZ twins were faster than MZ twins in reaching the moment for sit (p<0.001), crawl (p=0.013), stand (p<0.001) and walk (p<0.001), but not for turn.

Cohort

Between the five cohorts there were significant differences in the age of motor milestone achievement for turn (*p*<0.001), crawl (*p*<0.001), stand (*p*<0.001) and walk (*p*<0.001) as shown in Figure 1. For sit there were no significant cohort effects. For crawl, stand and walk, twins from the latest cohorts were slower in motor milestone achievement than twins from the first cohorts. Differences between cohort 1 and cohort 5 were at average 0.4 months for crawl, 0.5 months for walk and 0.8 months for stand. For turn the effects of cohort went up and down. Differences were 0.3 months (= 9 days) at the top.

Figure 1 shows the results of motor milestone achievement in months for MZ male (MZM), female (MZF) and DZ male (DZM), female (DZF) for each motor milestone by cohort. All results presented are with adjustment for GA. In all cohorts the age of milestone achievement was significantly higher for MZ for sit (*p*<0.001), crawl (*p*=0.015), stand (*p*<0.001) and walk (*p*=0.001) but not for turn. Differences were up to 10 days.

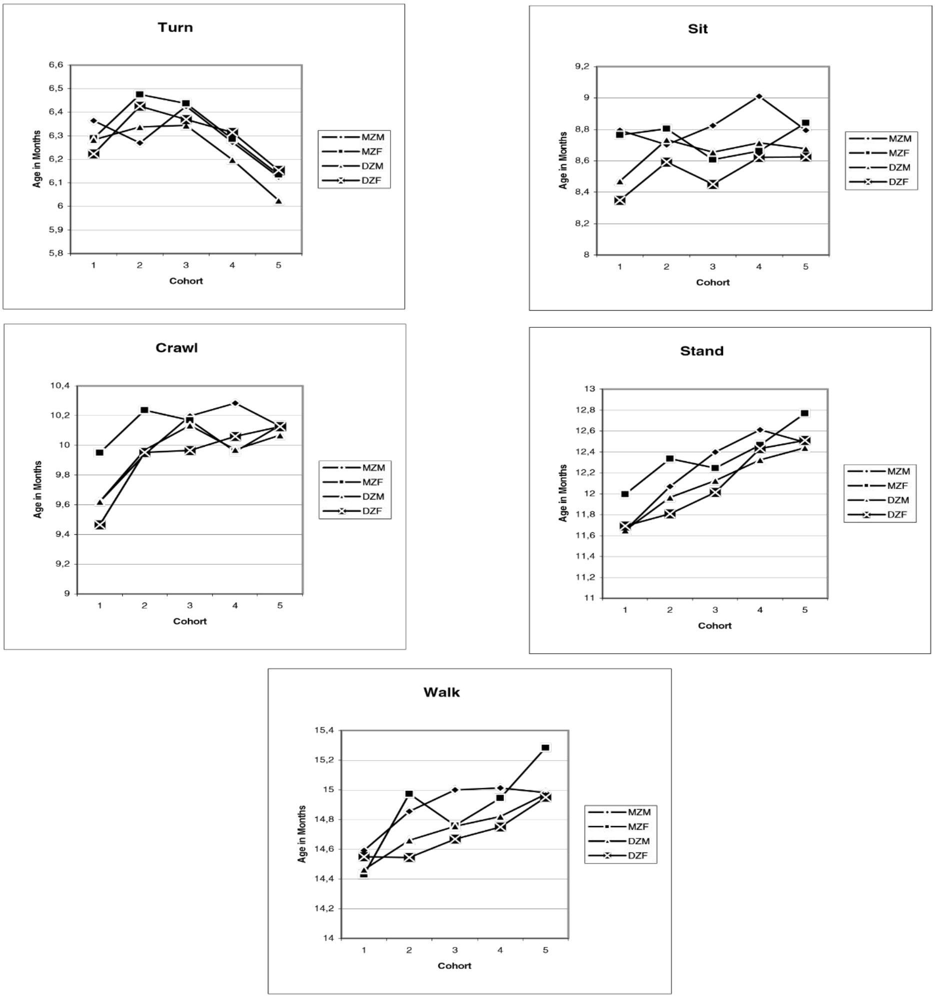

Figure 1

Motor milestone achievement in months for monozygotic male (MZM), female (MZF) and dizygotic male (DZM), female (DZF) by cohort.

Note: For each motor milestone (turn, sit, crawl, stand and walk) the means corrected for GA are reported in months for MZM, MZF, DZM and DZF (first-born twin). Dizygotic males/females are all males/females both from same-sex and opposite-sex twin pairs. For turn a decrease in months follows an increase from cohort 3 for all groups. For crawl, stand and walk an increase in months is reported by cohort for all groups.

DISCUSSION

Our data suggest that there are no remarkable differences between healthy singletons and healthy twins in the achievement of gross motor milestones within the normal range in the Netherlands. Within the standards that are used in CHC (9 months for turn; 12 months for sit; 15 months for crawl; 18 months for walk) over 90% of the twins reached the moment of attainment for the gross motor milestones. The group of twins from the NTR who participated in this study are comparable to the group of singletons from the SMOCC study. However, the assessment of the data was different in both studies. For the motor milestone achievement in twins, parents or caregivers were asked to report the information by questionnaire when the twins were 2 years old. For the singletons in the SMOCC study, parents or caregivers were asked by a physician or district nurse if a specific motor milestone was achieved at the moment of visiting the CHC.

The results of the comparison between the twins of the NTR and the singletons of the SMOCC study are in line with the study of Verkerk *et al*.[16] , which found that the frequency distribution of the SMOCC and reference values as used by Schlesinger-Was[15] differences were smaller than 10%. In a study of British twins born before 34 weeks GA[31], no differences were found between twins and singletons. However, a study of[32] reports that motor development during the first 18 months of life was delayed in Gambian twins compared to singletons for eight motor milestones. However, after adjustment for birthweight and number of siblings, singletons were ahead for three out of eight motor milestones (maintain head, sit and walk). As only children with a birthweight over 2500 grams were enrolled in the Gambian study and pairs with small GA and low birthweight were excluded, twins had a significant higher GA than singletons. Moreover, the study used the age of attainment of gross motor milestones for twins and singletons, which is more accurate than the comparison in our study, which uses the percentage of twins who reached a certain motor milestone by a fixed age. This is a possible explanation for the different results. Using just the percentage of twins who achieved a certain motor milestone can be less accurate but catches the development within the standard range for normal motor development.

There was a significant effect of GA on time of achieving the motor milestones. Twins born before term were prone to reach their milestones later than twins who are born at term. The correction for GA performed was consistent with the literature where several studies found that gross motor development needs to be corrected in the first 12 to 18 months of life[4-10,33]. Our study confirms earlier findings.

Except for reaching the moment for sitting without support, sex effects were not found. This is consistent with the findings of in studies in twins[7,34,35] which did not find sex effects on early motor development in preterm infants. However, it does not exclude that sex differences in motor development may emerge at later ages.

MZ twins were slower than DZ twins in reaching the moment for sit, crawl, stand and walk but not for turn. A possible explanation for the differences between MZ and DZ twins that remain in motor development after correction for GA is the greater vulnerability of MZ twins. But given the standard ranges for motor milestone achievement as used in CHC, Table 1 shows that MZ twins fall into the ranges of normal development. No differences were found for girls of the same sex compared to girls of opposite-sex twins. The same applies to boys. A second, behavioural possibility is that interaction is keener in DZ pairs. Observing your genetically different co-twin sit early may be motivating for infants, who use mimicry as a major form of communication. Although first-born twins were significantly faster than second-born twins in reaching the moment for turn and sit, but not for crawl, stand and walk, these differences were smaller than 1.5 days.

The effect of cohort on motor milestone achievement found in this study is remarkable. For crawl, stand and walk we found a significant effect of cohort, but the pattern was different with the pattern shown for turn. We noted an increase in time of achievement for crawl, stand and walk. Data shows that for crawl, stand and walk, twins in cohort 1 reached these milestones sooner than twins in cohort 5, which means a delay in motor development. Differences between cohorts were up to 14 days for crawl, 16 days for walk and 25 days for stand. For sit we did not find any effect of cohort. For turn the effect of cohort was significant. A delay was first seen from cohort 1 up to cohort 3. But from cohort 3 up to cohort 5 twins achieved the moment of turn faster. These data argue for delaying the moment of delivery, if possible, in order to minimize the effects of GA on the attainment of milestones.

In the CHC in the Netherlands the time delay in crawl, stand and walk will probably fall within the normal ranges because they do not register the time (in months) of achievement of motor milestones in children but rather score at fixed moments if motor milestones are reached. One possible explanation for the delay in crawl, stand and walk may be the sleep position which is recommended by family doctors in the CHC. In the early 1990s, CHC recommended that healthy infants should be positioned on their back for sleep to decrease the incidence of sudden infant death syndrome (SIDS). Our data, which show a delay starting in the 1990s, and different studies which show an effect of sleep position on motor development[22-27] which suggest that prone sleeping may have positive effects on the motor development. Dewey *et al.*[23] assume that the prone sleeper is stimulated to move and explore because the position itself is inherently boring and the child must do something to change these circumstances. Elaborating on this, Davis *et al*.[22] suggest that supine sleepers lag behind prone sleepers in milestones that require the use of upper trunk. This upper-extremity muscle development occurs routinely in infants who spend more time in the prone position. No unambiguous explanations are given for this phenomenon. Another explanation is the arrival of the babywalker, which also showed adverse effects on motor development[36] as babywalkers enable precocious locomotion in very young.

More detailed information and studies are necessary to find out if sleep position and other environmental changes cause structural effects of delay in the motor milestone achievement between cohorts. Therefore, it needs to be considered if structural delays have importance in a child's future development.

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